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(54) Title: SUBSTITUTED BIPHENYL-4-CARBOXYLIC ACID ARYLAMIDE ANALOGUES

(57) Abstract: Substituted biphenyl-4-carboxylic acid arylamide analogues capable of modulating receptor activity, are provided. Such ligands may be used to modulate receptor activity in vivo or in vitro, and are particularly useful in the treatment of pain and other conditions associated with receptor activation in humans, domesticated companion animals and livestock animals. Pharmaceutical compositions and methods for treating such disorders are provided, as are methods for using such ligands for receptor localization studies.

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10 Title: Substituted Biphenyl-4-Carboxylic Acid Arylamide Analogues

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SUBSTITUTED BIPHENYL-4-CARBOXYLIC ACID ARYLAMIDE ANALOGUES

FIELD OF THE INVENTION

5 This invention relates generally to substituted biphenyl-4-carboxylic acid arylamide analogues that are capsaicin receptor modulators, and to the use of such compounds for treating conditions related to capsaicin receptor activation. The invention further relates to the use of such compounds as probes for the detection and localization of capsaicin receptors.

CROSS-REFERENCE TO RELATED APPLICATIONS

10 This application claims priority to U.S. Provisional Application 60/435,118, filed December 19, 2002.

BACKGROUND OF THE INVENTION

15 Pain perception, or nociception, is mediated by the peripheral terminals of a group of specialized sensory neurons, termed "nociceptors." A wide variety of physical and chemical stimuli induce activation of such neurons in mammals, leading to recognition of a potentially harmful stimulus. Inappropriate or excessive activation of nociceptors, however, can result in debilitating acute or chronic pain.

20 Neuropathic pain involves pain signal transmission in the absence of stimulus, and typically results from damage to the nervous system. In most instances, such pain is thought to occur because of sensitization in the peripheral and central nervous systems following initial damage to the peripheral system (*e.g.*, via direct injury or systemic disease). Neuropathic pain is typically burning, shooting and unrelenting in its intensity and can sometimes be more debilitating than the initial injury or disease process that induced it.

25 Existing treatments for neuropathic pain are largely ineffective. Opiates, such as morphine, are potent analgesics, but their usefulness is limited because of adverse side effects, such as physical addictiveness and withdrawal properties, as well as respiratory depression, mood changes, and decreased intestinal motility with concomitant constipation, nausea, vomiting, and alterations in the endocrine and autonomic nervous systems. In
30 addition, neuropathic pain is frequently non-responsive or only partially responsive to conventional opioid analgesic regimens. Treatments employing the N-methyl-D-aspartate antagonist ketamine or the alpha(2)-adrenergic agonist clonidine can reduce acute or chronic pain, and permit a reduction in opioid consumption, but these agents are often poorly tolerated due to side effects.

Topical treatment with capsaicin has been used to treat chronic and acute pain, including neuropathic pain. Capsaicin is a pungent substance derived from the plants of the Solanaceae family (which includes hot chili peppers) and appears to act selectively on the small diameter afferent nerve fibers (A-delta and C fibers) that are believed to mediate pain.

5 The response to capsaicin is characterized by persistent activation of nociceptors in peripheral tissues, followed by eventual desensitization of peripheral nociceptors to one or more stimuli. From studies in animals, capsaicin appears to trigger C fiber membrane depolarization by opening cation selective channels for calcium and sodium. Capsaicin responses in isolated sensory neurons show dose-dependence.

10 Such responses are also evoked by structural analogues of capsaicin that share a common vanilloid moiety. One such analogue is resiniferatoxin (RTX), a natural product of *Euphorbia* plants. The term vanilloid receptor (VR) was coined to describe the neuronal membrane recognition site for capsaicin and such related irritant compounds. The capsaicin response is competitively inhibited (and thereby antagonized) by another capsaicin analog,

15 capsazepine, and is also inhibited by the non-selective cation channel blocker ruthenium red. These antagonists bind to VR with no more than moderate affinity (typically with K_i values of no lower than 140 μ M).

Recently, rat and human receptors for capsaicin were cloned from dorsal root ganglion cells. Such receptors have also been referred to as VR1, and the terms "VR1" and

20 "capsaicin receptor" are used interchangeably herein to refer to rat and/or human receptors of this type, as well as mammalian homologs. The role of VR1 in pain sensation has been confirmed using mice lacking this receptor, which exhibit no vanilloid-evoked pain behavior, and impaired responses to heat and inflammation. The capsaicin receptor is a nonselective cation channel with a threshold for opening that is lowered in response to elevated

25 temperatures, low pH, and capsaicin receptor agonists. For example, the channel usually opens at temperatures higher than about 45°C. Opening of the capsaicin receptor channel is generally followed by the release of inflammatory peptides from neurons expressing the receptor and other nearby neurons, increasing the pain response. After initial activation by capsaicin, the capsaicin receptor undergoes a rapid desensitization via phosphorylation by

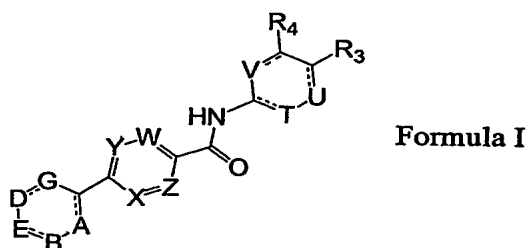
30 cAMP-dependent protein kinase.

Because of their ability to thus desensitize nociceptors in peripheral tissues, VR1 agonist vanilloid compounds have been used as topical anesthetics. However, agonist application may itself cause burning pain, which limits this therapeutic use.

Thus, compounds that interact with VR1 but do not elicit the initial painful sensation of VR1 agonist vanilloid compounds, are desirable for the treatment of chronic and acute pain, including neuropathic pain. Antagonists of this receptor are particularly desirable for the treatment of pain, as well as conditions such as tear gas exposure, itch and urinary incontinence. The present invention fulfills this need, and provides further related advantages.

SUMMARY OF THE INVENTION

The present invention provides VR1 modulators that alter, preferably inhibit, capsaicin receptor activity and/or activation. More specifically, within certain aspects, VR1 modulators provided herein are characterized by Formula I:



or a pharmaceutically acceptable form thereof, wherein:

each ---- independently represents a single or double bond;

either: (a) A, B and E are independently CR₁, C(R₁)₂, NR₁ or N; or

(b) B is joined with A or E to form a fused 5- to 8-membered partially saturated ring that is substituted with from 0 to 3 substituents independently selected from R₁, and the other of A or E is CR₁, C(R₁)₂, NR₁ or N;

D and G are independently CR₁, C(R₁)₂, NR₁ or N;

W, X, Y and Z are independently CR₁ or N;

T, U and V are independently CR₈, C(R₈)₂, N or NH;

R₁ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M;

R₃ and R₄ are:

(a) independently chosen from R₈; or

(b) taken together to form a fused ring selected from optionally substituted carbocyclic rings optionally substituted five-membered heterocyclic rings, optionally substituted seven membered rings or optionally substituted dioxane, or more preferably are taken together to form a fused ring selected from the group consisting of 5- to 8-membered

carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings and dioxane, each of which fused ring is substituted with from 0 to 3 substituents independently selected from halogen, hydroxy, amino, nitro, cyano, optionally substituted alkyl or more preferably C₁-C₆alkyl, optionally substituted alkenyl or more preferably C₂-C₆alkenyl, optionally substituted alkynyl or more preferably C₂-C₆alkynyl, optionally substituted haloalkyl or more preferably C₁-C₆haloalkyl, optionally substituted alkoxy or more preferably C₁-C₆alkoxy, optionally substituted haloalkoxy or more preferably C₁-C₆haloalkoxy, optionally substituted alkanoyl or more preferably C₁-C₆alkanoyl, optionally substituted alkyl ether or more preferably C₂-C₆alkyl ether, optionally substituted mono- and di-alkylamino and optionally substituted mono- and di-alkylamino-alkyl or more preferably mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, -optionally substituted *N*-alkylsulfonyl-amino or more preferably N(H)SO₂C₁-C₆alkyl, optionally substituted *N,N*-di(alkylsulfonyl)amino or more preferably -N(SO₂C₁-C₆alkyl)₂, and optionally substituted *N*-alkyl-*N*-alkylsulfonyl-amino or more preferably -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl;

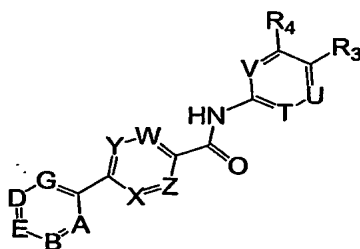
R₈ is independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, optionally substituted alkyl or more preferably C₁-C₆alkyl, optionally substituted haloalkyl or more preferably C₁-C₆haloalkyl, optionally substituted alkoxy or more preferably C₁-C₆alkoxy, optionally substituted haloalkoxy or more preferably C₁-C₆haloalkoxy, optionally substituted alkanoyl or more preferably C₁-C₆alkanoyl, optionally substituted alkyl ether or more preferably C₂-C₆alkyl ether, optionally substituted mono- and di-alkylamino or more preferably mono- and di-(C₁-C₆alkyl)amino, optionally substituted *N*-alkylsulfonyl-amino or more preferably -N(H)SO₂C₁-C₆alkyl, optionally substituted *N,N*-di(alkylsulfonyl)amino or more preferably -N(SO₂C₁-C₆alkyl)₂, optionally substituted *N*-alkyl-*N*-alkylsulfonyl-amino or more preferably -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl, and optionally substituted heterocycle or more preferably 5 to 7 membered heteroalicyclic and heteroaryl rings;

L is independently chosen at each occurrence from a bond, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, S(O)_m, N(R_x), C(=O)N(R_x), N(R_x)C(=O), N(R_x)S(O)_m, S(O)_mN(R_x) and N[S(O)_mR_x]S(O)_m; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C₁-C₈alkyl; and

M is independently selected at each occurrence from (a) hydrogen; and (b) optionally substituted alkyl or more preferably C₁-C₈alkyl, optionally substituted alkenyl or more

preferably C₂-C₈alkenyl, optionally substituted alkynyl or more preferably C₂-C₈alkynyl, optionally substituted mono- and di-alkylamino and optionally substituted mono- and di-(alkylamino)alkyl or more preferably mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), optionally substituted phenyl and optionally substituted phenyl-alkyl or more preferably phenylC₀-C₄alkyl and optionally substituted heterocycle and optionally substituted heterocycle-alkyl or more preferably (5- to 6-membered heterocycle)C₀-C₄alkyl, each of which is substituted with from 0 to 5 substituents independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, aminocarbonyl, aminoC₁-C₆alkyl and mono- and di-(C₁-C₆alkyl)amino.

Certain such compounds satisfy Formula Ia:



Formula Ia

wherein the variables are as described above, except that:

either: (a) A, B and E are independently CR₁ or N; or

(b) B is joined with A or E to form a fused 5- to 8-membered partially saturated ring that is substituted with from 0 to 3 substituents independently selected from R₁, and

the other of A or E is CR₁ or N;

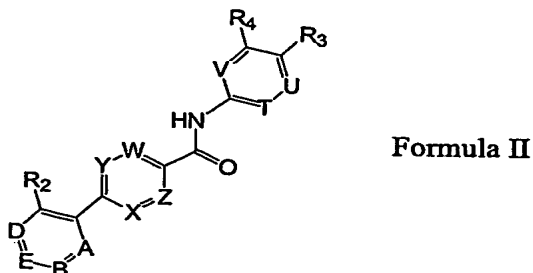
D, G, W, X, Y and Z are independently CR₁ and N;

T, U and V are independently CR₈ or N; and

M is independently selected at each occurrence from (a) hydrogen; and (b) optionally substituted alkyl or more preferably C₁-C₈alkyl, optionally substituted alkenyl or more preferably C₂-C₈alkenyl, optionally substituted alkynyl or more preferably C₂-C₈alkynyl, optionally substituted mono- and di-alkylamino and optionally substituted mono- and di-(alkylamino)alkyl or more preferably mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), optionally substituted phenyl and optionally substituted phenyl-alkyl or more preferably phenylC₀-C₄alkyl, optionally substituted heteroaryl and optionally substituted heteroaryl-alkyl or more preferably (5-membered heteroaryl)C₀-C₄alkyl, and optionally substituted heterocycloalkyl and optionally substituted heterocycloalkyl-alkyl or more preferably (5- to 7-membered heterocycloalkyl)C₀-C₄alkyl, each of which is substituted with from 0 to 5 substituents independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, C₁-

C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, aminocarbonyl, aminoC₁-C₆alkyl and mono- and di-(C₁-C₆alkyl)amino.

Within further aspects, certain compounds of Formula I further satisfy Formula II:



wherein:

5 A, B, D, E, W, X, Y and Z are independently CR₁ or N;

T, U and V are independently CR₈ or N;

R₁ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L_a-R_a;

10 R₂ is selected from nitro, cyano, -NHOH, and groups of the formula L_a-R_a; with the proviso that R₂ is not hydrogen;

R₃ and R₄ are:

(a) each independently selected from (i) hydrogen and halogen; and (ii) optionally substituted alkyl or more preferably C₁-C₈alkyl, optionally substituted alkyl ether or more preferably C₂-C₈alkyl ether, optionally substituted alkylsulfonyl or more preferably -SO₂C₁-C₆alkyl, and optionally substituted heterocycle or more preferably 5 to 7 membered heteroalicyclic and heteroaryl rings, each of which is substituted with from 0 to 5 substituents independently chosen from halogen, hydroxy, amino, cyano and nitro; with the proviso that at least one of R₃ and R₄ is not hydrogen; or

20 (b) taken together to form a fused ring selected from 5- to 8-membered carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings; and dioxane, wherein each fused ring is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, nitro, cyano, C₁-C₆alkyl and C₁-C₆haloalkyl;

R₈ is independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, optionally substituted alkyl or more preferably C₁-C₆alkyl, optionally substituted haloalkyl or more preferably C₁-C₆haloalkyl, optionally substituted alkoxy or more preferably C₁-C₆alkoxy, optionally substituted haloalkoxy or more preferably C₁-C₆haloalkoxy, optionally substituted alkanoyl or more preferably C₁-C₆alkanoyl, optionally substituted alkyl ether or more preferably C₂-C₆alkyl ether, optionally

substituted mono- and di-alkylamino or more preferably mono- and di-(C₁-C₆alkyl)amino, optionally substituted *N*-alkylsulfonyl-amino or more preferably -N(H)SO₂C₁-C₆alkyl, optionally substituted *N,N*-di(alkylsulfonyl)amino or more preferably -N(SO₂C₁-C₆alkyl)₂ and *N*-alkyl-*N*-alkylsulfonyl-amino or more preferably -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl;

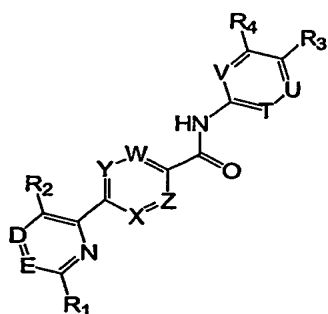
L_a is independently chosen at each occurrence from a bond, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, S(O)_m, N(R_x), N(R_x)C(=O), N(R_x)S(O)_m, S(O)_mN(R_x) and N[S(O)_mR_x]S(O)_m; wherein *m* is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C₁-C₈alkyl; and

R_a is independently selected at each occurrence from:

(a) hydrogen; and

(b) optionally substituted alkyl or more preferably C₁-C₈alkyl, optionally substituted alkenyl or more preferably C₂-C₈alkenyl, optionally substituted alkynyl or more preferably C₂-C₈alkynyl, optionally substituted mono- and di-alkylamino and optionally substituted mono- and di-(alkylamino)alkyl or more preferably mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), optionally substituted heteroaryl and optionally substituted heteroaryl-alkyl or more preferably (5-membered heteroaryl)C₀-C₄alkyl, and optionally substituted heterocycloalkyl and optionally substituted heterocycloalkyl-alkyl or more preferably (5- to 7-membered heterocycloalkyl)C₀-C₄alkyl, each of which is substituted with from 0 to 5 substituents, independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, aminocarbonyl, aminoC₁-C₆alkyl, and mono- and di-(C₁-C₆alkyl)amino.

Within other aspects, certain compounds of Formula I further satisfy Formula III:



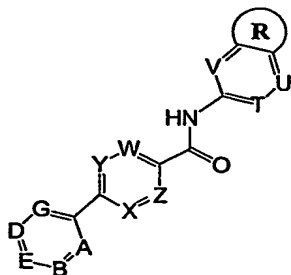
Formula III

wherein:

D, E, T, U, V, W, X, Y, Z, R₁, R₃ and R₄ are as described for Formula I or Formula Ia;

R_2 is halogen, cyano, nitro or a group of the formula L-M as described for Formula I or Formula Ia; with the proviso that R_2 is not hydrogen.

Within further aspects, certain compounds of Formula I further satisfy Formula IV:



Formula IV

wherein:

- 5 A, B, E, D and G are independently CH, CR_7 or N; with the proviso that at least one of G, D and E is CR_7 ;

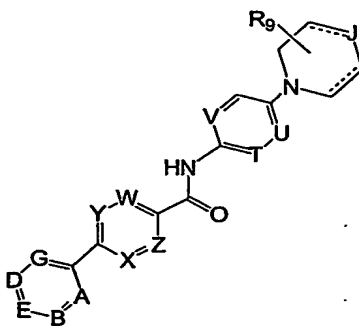
T, U, V, W, X, Y and Z are as described for Formula I or Formula Ia;

- 10 \textcircled{R} represents a fused 5- or 7-membered carbocyclic or heterocyclic ring or a fused dioxane ring, wherein the fused ring is substituted with from 0 to 3 substituents independently selected from oxo, halogen, hydroxy, amino, cyano, nitro, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy and C_1 - C_4 haloalkoxy;

R_7 is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M; with the proviso that R_7 is not hydrogen; and

each L and M is as described for Formula I or Formula Ia.

- 15 Within still further aspects, certain compounds of Formula I further satisfy Formula V:



Formula V

wherein:

J is N, NH, O or S;

- 20 A, B, E, D and G are independently CH, CR_7 or N; with the proviso that at least one of G, D and E is CR_7 ;

W, X, Y and Z are independently CR₁ or N;

T, U and V are independently CR₈ or N;

R₁ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-R_a;

5 R₇ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-R_a, with the proviso that R₇ is not hydrogen;

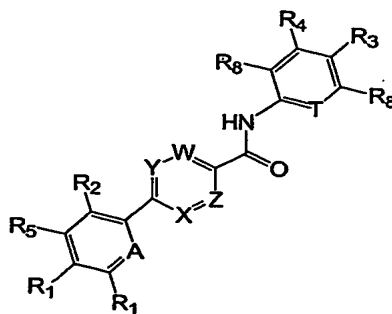
R₈ is independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, optionally substituted alkyl or more preferably C₁-C₆alkyl, optionally substituted haloalkyl or more preferably C₁-C₆haloalkyl, optionally substituted alkoxy or more preferably C₁-C₆alkoxy, optionally substituted haloalkoxy or more preferably C₁-C₆haloalkoxy, optionally substituted alkanoyl or more preferably C₁-C₆alkanoyl, optionally substituted alkyl ether or more preferably C₂-C₆alkyl ether, optionally substituted mono- and di-alkylamino or more preferably mono- and di-(C₁-C₆alkyl)amino, optionally substituted *N*-(alkylsulfonyl)amino or more preferably -
 10 N(H)SO₂C₁-C₆alkyl), optionally substituted *N,N*-di(alkylsulfonyl)amino or more preferably -
 15 N(H)SO₂C₁-C₆alkyl), optionally substituted *N,N*-di(alkylsulfonyl)amino or more preferably -
 N(SO₂C₁-C₆alkyl)₂ and *N*-alkyl-*N*-alkylsulfonyl-amino or more preferably -
 N(C₁-C₆alkyl)SO₂C₁-C₆alkyl;

R₉ represents from 0 to 2 substituents independently chosen from halogen, cyano, nitro, optionally substituted alkyl or more preferably C₁-C₄alkyl, optionally substituted alkoxy or more preferably C₁-C₄alkoxy, optionally substituted haloalkyl or more preferably C₁-C₄haloalkyl, optionally substituted haloalkoxy or more preferably C₁-C₄haloalkoxy, optionally substituted mono- and di-alkylamino or more preferably mono- and di-(C₁-C₆alkyl)amino, and optionally substituted alkyl ether or more preferably C₂-C₆alkyl ether;

L is as described for Formula I; and

25 R_a is as described for Formula II.

Within other aspects, certain compounds of Formula I further satisfy Formula VI:



Formula VI

wherein:

A, T, W, X, Y, Z are independently CR₁ or N;

each R₁ is independently chosen from hydrogen, halogen, hydroxy, amino, cyano, nitro, optionally substituted alkyl or more preferably C₁-C₄alkyl, optionally substituted alkoxy C₁-C₄alkoxy, optionally substituted haloalkyl or more preferably C₁-C₄haloalkyl and optionally substituted haloalkoxy or more preferably C₁-C₄haloalkoxy;

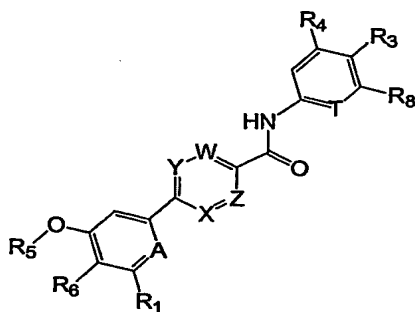
either: (a) R₂ is a halogen and R₅ is hydrogen; or (b) R₂ is hydrogen and R₅ is a halogen; and with regard to R₃ and R₄:

(a) R₃ is C₁-C₆alkyl and R₄ is hydrogen, halogen, hydroxy, amino, cyano, optionally substituted alkyl or more preferably C₁-C₄alkyl, optionally substituted alkoxy or more preferably C₁-C₄alkoxy, optionally substituted haloalkyl or more preferably C₁-C₄haloalkyl or optionally substituted haloalkoxy C₁-C₄haloalkoxy;

(b) R₃ is hydrogen, halogen, amino, cyano or optionally substituted alkoxy or more preferably C₁-C₄alkoxy; and R₄ is halogen, hydroxy, amino, cyano, optionally substituted alkyl or more preferably C₁-C₄alkyl or optionally substituted alkoxy C₁-C₄alkoxy; or

(c) R₃ and R₄ are taken together to form a 5- or 6-membered partially saturated carbocycle substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, cyano, nitro, oxo, C₁-C₄alkyl and C₁-C₄alkoxy.

Within other aspects, certain compounds of Formula I further satisfy Formula VII:



Formula VII

wherein:

A and T are independently CH or N;

W, X, Y and Z are independently CR₁ or N;

R₁ and R₈ are independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, optionally substituted alkyl or more preferably C₁-C₄alkyl, optionally substituted alkoxy or more preferably C₁-C₄alkoxy, optionally substituted haloalkyl or more preferably C₁-C₄haloalkyl and optionally substituted haloalkoxy or more preferably C₁-C₄haloalkoxy;

R₃ and R₄ are:

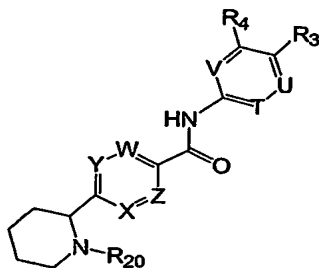
(a) independently chosen from hydrogen, halogen, hydroxy, amino, cyano, optionally substituted alkyl or more preferably C₁-C₄alkyl, optionally substituted alkoxy or more preferably C₁-C₄alkoxy, optionally substituted haloalkyl or more preferably C₁-C₄haloalkyl, optionally substituted haloalkoxy or more preferably C₁-C₄haloalkoxy, and optionally substituted heterocycle or more preferably 5 to 7 membered heteroalicyclic and heteroaryl rings; or

(b) taken together to form a fused ring chosen from 5- to 7-membered partially saturated carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings and dioxane, wherein fused ring is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, cyano, nitro, oxo, C₁-C₄alkyl and C₁-C₄alkoxy;

R₅ is: (a) optionally substituted alkyl or more preferably C₁-C₆alkyl, optionally substituted haloalkyl or more preferably C₁-C₆haloalkyl, optionally substituted alkenyl or more preferably C₁-C₆alkenyl or optionally substituted alkynyl or more preferably C₁-C₆alkynyl; or (b) taken together with R₆ to form a fused 5- to 7-membered partially saturated heterocycle; and

R₆ is (a) hydrogen, halogen, hydroxy, amino, cyano, nitro, optionally substituted alkyl or more preferably C₁-C₄alkyl, optionally substituted alkoxy or more preferably C₁-C₄alkoxy, optionally substituted haloalkyl or more preferably C₁-C₄haloalkyl or optionally substituted haloalkoxy or more preferably C₁-C₄haloalkoxy; or (b) taken together with R₅ to form a fused 5- to 7-membered partially saturated heterocycle.

Within further aspects, certain compounds of Formula I further satisfy Formula VIII:



Formula VIII

wherein:

T, U, V, W, X, Y and Z are independently CR₁ or N;

R₁ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M; wherein L and M are as described for Formula I or Formula Ia; and

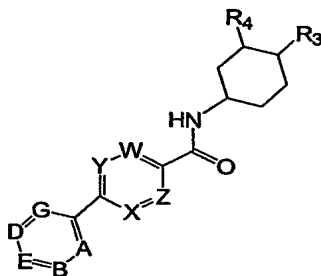
R₃ and R₄ are:

(a) independently chosen from R₁; or

(b) taken together to form a fused ring selected from 5- to 8-membered carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings and dioxane, each of which fused ring is substituted with from 0 to 3 substituents independently selected from halogen, hydroxy, amino, nitro, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂ and -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl;

R₂₀ is hydrogen, optionally substituted alkyl or more preferably C₁-C₆alkyl, optionally substituted alkanoyl or more preferably C₁-C₆alkanoyl or optionally substituted alkylsulfonyl or more preferably -SO₂C₁-C₆alkyl.

Within still further aspects, certain compounds of Formula I further satisfy Formula IX:



Formula IX

wherein:

A, B, E, D, G, W, X, Y and Z are independently CR₁ or N;

R₃ and R₄ are independently chosen from R₁; and

R₁ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M; wherein L and M are as described for Formula I or Formula Ia.

Pharmaceutically acceptable forms of compounds of Formulas II-IX are also provided.

Within certain aspects, VR1 modulators as described herein exhibit a K_i of no greater than 1 micromolar, 100 nanomolar, 50 nanomolar, 10 nanomolar or 1 nanomolar in a capsaicin receptor binding assay and/or have an EC₅₀ or IC₅₀ value of no greater than 1 micromolar, 100 nanomolar, 50 nanomolar, 10 nanomolar or 1 nanomolar in an assay for determination of capsaicin receptor antagonist or agonist activity. Preferred compounds are generally those with higher potency (*i.e.*, lower K_i or lower EC₅₀ or IC₅₀).

In certain embodiments, VR1 modulators as described herein are VR1 antagonists and exhibit no detectable agonist activity in an *in vitro* assay of capsaicin receptor activation.

Within certain aspects, VR1 modulators as described herein are labeled with a detectable marker (*e.g.*, radiolabeled or fluorescein conjugated).

The present invention further provides, within other aspects, pharmaceutical compositions comprising at least VR1 modulator as described herein in combination with a
5 physiologically acceptable carrier or excipient.

Within further aspects, methods are provided for reducing calcium conductance of a cellular capsaicin receptor, comprising contacting a cell (*e.g.*, neuronal) expressing a capsaicin receptor with a capsaicin receptor modulatory amount of at least one VR1 modulator as described herein. Such contact may occur *in vivo* or *in vitro*.

10 Methods are further provided for inhibiting binding of vanilloid ligand to a capsaicin receptor. Within certain such aspects, the inhibition takes place *in vitro*. Such methods comprise contacting a capsaicin receptor with at least one VR1 modulator as described herein, under conditions and in an amount sufficient to detectably inhibit vanilloid ligand binding to the capsaicin receptor. Within other such aspects, the capsaicin receptor is in a
15 patient. Such methods comprise contacting cells expressing a capsaicin receptor in a patient with at least one VR1 modulator as described herein in an amount sufficient to detectably inhibit vanilloid ligand binding to cells expressing a cloned capsaicin receptor *in vitro*, and thereby inhibiting binding of vanilloid ligand to the capsaicin receptor in the patient.

The present invention further provides methods for treating a condition responsive to
20 capsaicin receptor modulation in a patient, comprising administering to the patient a capsaicin receptor modulatory amount of at least one VR1 modulator as described herein.

Within other aspects, methods are provided for treating pain in a patient, comprising administering to a patient suffering from pain a capsaicin receptor modulatory amount of at least one VR1 modulator as described herein.

25 Methods are further provided for treating itch, urinary incontinence, cough and/or hiccup in a patient, comprising administering to a patient suffering from one or more of the foregoing conditions a capsaicin receptor modulatory amount of at least one VR1 modulator as described herein.

The present invention further provides methods for promoting weight loss in an obese
30 patient, comprising administering to an obese patient a capsaicin receptor modulatory amount of at least one VR1 modulator as described herein.

Within further aspects, the present invention provides methods for determining the presence or absence of capsaicin receptor in a sample, comprising: (a) contacting a sample

with a compound as described herein under conditions that permit binding of the compound to capsaicin receptor; and (b) detecting a level of the compound bound to capsaicin receptor.

The present invention also provides packaged pharmaceutical preparations, comprising: (a) a pharmaceutical composition as described herein in a container; and (b) instructions for using the composition to treat one or more conditions responsive to capsaicin receptor modulation, such as pain, itch, urinary incontinence, cough, hiccup, and/or obesity.

In yet another aspect, the invention provides methods for preparing the compounds disclosed herein, including the intermediates.

These and other aspects of the present invention will become apparent upon reference to the following detailed description.

DETAILED DESCRIPTION

As noted above, the present invention provides VR1 modulators that are substituted biphenyl-4-carboxylic acid arylamide analogues. Such modulators may be used *in vitro* or *in vivo*, to modulate capsaicin receptor activity in a variety of contexts.

TERMINOLOGY

Compounds are generally described herein using standard nomenclature. For compounds having asymmetric centers, it should be understood that (unless otherwise specified) all of the optical isomers and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E- forms, with all isomeric forms of the compounds being included in the present invention unless otherwise specified. Where a compound exists in various tautomeric forms, a recited compound is not limited to any one specific tautomer, but rather is intended to encompass all tautomeric forms. Certain compounds are described herein using a general formula that includes variables (*e.g.*, R₁, A, Z). Unless otherwise specified, each variable within such a formula is defined independently of any other variable, and any variable that occurs more than one time in a formula is defined independently at each occurrence.

The term "substituted biphenyl-4-carboxylic acid arylamide analogue," as used herein, encompasses all compounds of Formula I, Ia and/or any of subformulas II-IX, including any enantiomers, racemates and stereoisomers. Pharmaceutically acceptable forms of such compounds are also encompassed by the term "substituted biphenyl-4-carboxylic acid arylamide analogues."

"Pharmaceutically acceptable forms" of the compounds recited herein are pharmaceutically acceptable salts, hydrates, solvates, crystal forms, polymorphs, chelates, non-covalent complexes, esters, clathrates and prodrugs of such compounds. As used herein, a pharmaceutically acceptable salt is an acid or base salt that is generally considered in the art to be suitable for use in contact with the tissues of human beings or animals without excessive toxicity, irritation, allergic response, or other problem or complication. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic acids. Specific pharmaceutical salts include, but are not limited to, salts of acids such as hydrochloric, phosphoric, hydrobromic, malic, glycolic, fumaric, sulfuric, sulfamic, sulfanilic, formic, toluenesulfonic, methanesulfonic, benzene sulfonic, ethane disulfonic, 2-hydroxyethylsulfonic, nitric, benzoic, 2-acetoxybenzoic, citric, tartaric, lactic, stearic, salicylic, glutamic, ascorbic, pantoic, succinic, fumaric, maleic, propionic, hydroxymaleic, hydroiodic, phenylacetic, alkanolic such as acetic, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and the like. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium. Those of ordinary skill in the art will recognize further pharmaceutically acceptable salts for the compounds provided herein, including those listed by *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, p. 1418 (1985). In general, a pharmaceutically acceptable acid or base salt can be synthesized from a parent compound that contains a basic or acidic moiety by any conventional chemical method. Briefly, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, the use of nonaqueous media, such as ether, ethyl acetate, ethanol, isopropanol or acetonitrile, is preferred.

A "prodrug" is a compound that may not fully satisfy the structural requirements of the compounds provided herein, but is modified *in vivo*, following administration to a patient, to produce a compound of Formula I, Ia or subformulas II-IX. For example, a prodrug may be an acylated derivative of a compound as provided herein. Prodrugs include compounds wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein. Prodrugs of the compounds provided herein may be prepared by modifying

functional groups present in the compounds in such a way that the modifications are cleaved to the parent compounds.

As used herein, the term "alkyl" refers to a straight chain, branched chain or cyclic saturated aliphatic hydrocarbon. An alkyl group may be bonded to an atom within a molecule of interest via any chemically suitable portion. Alkyl groups include groups having from 1 to 8 carbon atoms (C₁-C₈alkyl), from 1 to 6 carbon atoms (C₁-C₆alkyl) and from 1 to 4 carbon atoms (C₁-C₄alkyl), such as methyl, ethyl, propyl, isopropyl, n-butyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, 3-methylpentyl, cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cycloheptyl and norbornyl. "C₀-C₄alkyl" refers to a bond or an alkyl group having 1, 2, 3 or 4 carbon atoms; "C₀-C₆alkyl" refers to a bond or a C₁-C₆alkyl group; "C₀-C₈alkyl" refers to a bond or a C₁-C₈alkyl group. In certain embodiments, preferred alkyl groups are straight or branched chain. In some instances herein, a substituent of an alkyl group is specifically indicated. For example, "C₁-C₄hydroxyalkyl" refers to a C₁-C₄alkyl group that has at least one -OH substituent. "AminoC₀-C₄alkyl" refers to an amino group or a C₁-C₄alkyl group that has at least one -NH₂ substituent.

Similarly, "alkenyl" refers to straight or branched chain alkene groups or cycloalkene groups, in which at least one unsaturated carbon-carbon double bond is present. Alkenyl groups include C₂-C₈alkenyl, C₂-C₆alkenyl and C₂-C₄alkenyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively, such as ethenyl, allyl or isopropenyl. "Alkynyl" refers to straight or branched chain alkyne groups, which have one or more unsaturated carbon-carbon bonds, at least one of which is a triple bond. Alkynyl groups include C₂-C₈alkynyl, C₂-C₆alkynyl and C₂-C₄alkynyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively. In certain embodiments, preferred alkenyl and alkynyl groups are straight or branched chain.

By "alkoxy," as used herein, is meant an alkyl, alkenyl or alkynyl group as described above attached via an oxygen bridge. Alkoxy groups include C₁-C₈alkoxy, C₁-C₆alkoxy and C₁-C₄alkoxy groups, which have from 1 to 8, 1 to 6 or 1 to 4 carbon atoms, respectively. Alkoxy groups include, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, *sec*-butoxy, *tert*-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy. Similarly, "alkylthio" refers to an alkyl, alkenyl or alkynyl group as described above attached via a sulfur bridge. Preferred alkoxy and alkylthio groups are those in which an alkyl group is attached via the heteroatom bridge.

The term "alkanoyl" refers to an acyl group in a linear, branched or cyclic arrangement (*e.g.*, $-(C=O)-alkyl$). Alkanoyl groups include C_2-C_8 alkanoyl, C_2-C_6 alkanoyl and C_2-C_4 alkanoyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively. " C_1 alkanoyl" refers to $-(C=O)-H$, which (along with C_2-C_8 alkanoyl) is encompassed by the term " C_1-C_8 alkanoyl."

An "alkanone" is a ketone group in which carbon atoms are in a linear, branched or cyclic alkyl arrangement. " C_3-C_8 alkanone," " C_3-C_6 alkanone" and " C_3-C_4 alkanone" refer to an alkanone having from 3 to 8, 6 or 4 carbon atoms, respectively. By way of example, a C_3 alkanone group has the structure $-CH_2-(C=O)-CH_3$.

Similarly, "alkyl ether" refers to a linear or branched ether substituent linked via a carbon-carbon bond. Alkyl ether groups include C_2-C_8 alkyl ether, C_2-C_6 alkyl ether and C_2-C_4 alkyl ether groups, which have 2 to 8, 6 or 4 carbon atoms, respectively. By way of example, a C_2 alkyl ether group has the structure $-CH_2-O-CH_3$.

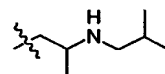
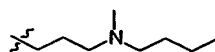
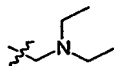
The term "alkoxycarbonyl" refers to an alkoxy group linked via a carbonyl (*i.e.*, a group having the general structure $-C(=O)-O-alkyl$). Alkoxycarbonyl groups include C_2-C_8 , C_2-C_6 and C_2-C_4 alkoxycarbonyl groups, which have from 2 to 8, 6 or 4 carbon atoms, respectively. " C_1 alkoxycarbonyl" refers to $-C(=O)-OH$, which is encompassed by the term " C_1-C_8 alkoxycarbonyl."

"Alkanoyloxy," as used herein, refers to an alkanoyl group linked via an oxygen bridge (*i.e.*, a group having the general structure $-O-C(=O)-alkyl$). Alkanoyloxy groups include C_2-C_8 , C_2-C_6 and C_2-C_4 alkanoyloxy groups, which have from 2 to 8, 6 or 4 carbon atoms, respectively. " C_1 alkanoyloxy" refers to $O-C(=O)-H$, which is encompassed by the term " C_1-C_8 alkanoyloxy."

"Alkylamino" refers to a secondary or tertiary amine having the general structure $-NH-alkyl$ or $-N(alkyl)(alkyl)$, wherein each alkyl may be the same or different. Such groups include, for example, mono- and di- (C_1-C_8alkyl) amino groups, in which each alkyl may be the same or different and may contain from 1 to 8 carbon atoms, as well as mono- and di- (C_1-C_6alkyl) amino groups and mono- and di- (C_1-C_4alkyl) amino groups. $(C_5-C_6cycloalkyl)$ amino refers to mono-alkylamino groups in which the alkyl is cyclopentyl or cyclohexyl.

"Alkylaminoalkyl" refers to an alkylamino group linked via an alkyl group (*i.e.*, a group having the general structure $-alkyl-NH-alkyl$ or $-alkyl-N(alkyl)(alkyl)$) in which each alkyl is selected independently. Such groups include, for example, mono- and di- (C_1-C_8alkyl) amino C_1-C_8alkyl , mono- and di- (C_1-C_6alkyl) amino C_1-C_6alkyl and mono- and di- $(C_1-$

C₄alkyl)aminoC₁-C₄alkyl, in which each alkyl may be the same or different. "Mono- or di-(C₁-C₆alkyl)aminoC₀-C₆alkyl" refers to a mono- or di-(C₁-C₆alkyl)amino group linked via a direct bond or a C₁-C₆alkyl group. The following are representative alkylaminoalkyl groups:



5 The term "aminocarbonyl" refers to an amide group (*i.e.*, -(C=O)NH₂).

The term "oxo," as used herein, refers to a keto (C=O) group. An oxo group that is a substituent of a nonaromatic ring results in a conversion of -CH₂- to -C(=O)-. It will be apparent that the introduction of an oxo substituent on an aromatic ring destroys the aromaticity.

10 The term "halogen" refers to fluorine, chlorine, bromine and iodine.

A "haloalkyl" is a branched, straight-chain or cyclic alkyl group, substituted with 1 or more halogen atoms (*e.g.*, "haloC₁-C₈alkyl" groups have from 1 to 8 carbon atoms; "haloC₁-C₆alkyl" groups have from 1 to 6 carbon atoms). Examples of haloalkyl groups include, but are not limited to, mono-, di- or tri-fluoromethyl; mono-, di- or tri-chloromethyl; mono-, di-, tri-, tetra- or penta-fluoroethyl; mono-, di-, tri-, tetra- or penta-chloroethyl; and 1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl. Typical haloalkyl groups are trifluoromethyl and difluoromethyl. The term "haloalkoxy" refers to a haloalkyl group as defined above attached via an oxygen bridge. "HaloC₁-C₈alkoxy" groups have 1 to 8 carbon atoms.

20 A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -CONH₂ is attached through the carbon atom.

A "heteroatom," as used herein, is oxygen, sulfur or nitrogen.

A "carbocycle" or "carbocyclic group" comprises at least one ring formed entirely by carbon-carbon bonds (referred to herein as a carbocyclic ring), and does not contain a heterocyclic ring. Unless otherwise specified, each carbocyclic ring within a carbocycle may be saturated, partially saturated or aromatic. A carbocycle generally has from 1 to 3 fused, pendant or spiro rings; carbocycles within certain embodiments have one ring or two fused rings. Typically, each ring contains from 3 to 8 ring members (*i.e.*, C₃-C₈); C₅-C₇ rings are recited in certain embodiments. Carbocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Certain representative carbocycles are cycloalkyl (*i.e.*, groups that comprise saturated and/or partially saturated rings, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, decahydro-naphthalenyl, octahydro-indenyl, and partially saturated variants of any of the

foregoing, such as cyclohexenyl). Other carbocycles are aryl (*i.e.*, contain at least one aromatic carbocyclic ring). Such carbocycles include, for example, phenyl, naphthyl, fluorenyl, indanyl and 1,2,3,4-tetrahydro-naphthyl.

Certain carbocycles recited herein are C₆-C₁₀arylC₀-C₈alkyl groups (*i.e.*, groups in which a carbocyclic group comprising at least one aromatic ring is linked via a direct bond or a C₁-C₈alkyl group). Such groups include, for example, phenyl and indanyl, as well as groups in which either of the foregoing is linked via C₁-C₈alkyl, preferably via C₁-C₄alkyl. Phenyl groups linked via a direct bond or alkyl group may be designated phenylC₀-C₈alkyl (*e.g.*, benzyl, 1-phenyl-ethyl, 1-phenyl-propyl and 2-phenyl-ethyl). A phenylC₀-C₈alkoxy group is a phenyl ring linked via an oxygen bridge or an alkoxy group having from 1 to 8 carbon atoms (*e.g.*, phenoxy or benzoxy).

A "heterocycle" or "heterocyclic group" has from 1 to 3 fused, pendant or spiro rings, at least one of which is a heterocyclic ring (*i.e.*, one or more ring atoms is a heteroatom, with the remaining ring atoms being carbon). Typically, a heterocyclic ring comprises 1, 2, 3 or 4 heteroatoms; within certain embodiments each heterocyclic ring has 1 or 2 heteroatoms per ring. Each heterocyclic ring generally contains from 3 to 8 ring members (rings having from 4 or 5 to 7 ring members are recited in certain embodiments) and heterocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Certain heterocycles comprise a sulfur atom as a ring member; in certain embodiments, the sulfur atom is oxidized to SO or SO₂. Heterocycles may be optionally substituted with a variety of substituents, as indicated. Unless otherwise specified, a heterocycle may be a heterocycloalkyl group (*i.e.*, each ring is saturated or partially saturated) or a heteroaryl group (*i.e.*, at least one ring within the group is aromatic). A heterocyclic group may generally be linked via any ring or substituent atom, provided that a stable compound results. N-linked heterocyclic groups are linked via a component nitrogen atom.

Heterocyclic groups include, for example, azepanyl, azocinyl, benzimidazolyl, benzimidazolinyl, benzisothiazolyl, benzisoxazolyl, benzofuranyl, benzothiofuranyl, benzoxazolyl, benzothiazolyl, benztetrazolyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, dihydrofuro[2,3-b]tetrahydrofuranyl, dihydroisoquinolinyl, dihydrotetrahydrofuranyl, 1,4-dioxo-8-aza-spiro[4.5]decyl, dithiazinyl, furanyl, furazanyl, imidazolyl, imidazolidinyl, imidazolyl, indazolyl, indolenyl, indolinyl, indoliziny, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isothiazolyl, isoxazolyl, isoquinolinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, oxazolidinyl, oxazolyl, phthalazinyl, piperazinyl, piperidinyl, piperidinyl, piperidonyl,

pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridoimidazolyl, pyridooxazolyl, pyridothiazolyl, pyridyl, pyrimidyl, pyrrolidinyl, pyrrolidonyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, quinuclidinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thiadiazinyl, thiadiazolyl, thiazolyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thienyl, thiophenyl, thiomorpholinyl and variants thereof in which the sulfur atom is oxidized, triazinyl, and any of the foregoing that are substituted with from 1 to 4 substituents as described above.

A "heterocycleC₀-C₈alkyl" is a heterocyclic group linked via a direct bond or C₁-C₈alkyl group. A (5- to 10-membered heterocycle)C₀-C₈alkyl is a heterocyclic group having from 5 to 10 ring members linked via a direct bond or an alkyl group having from 1 to 8 carbon atoms. If the heterocycle is heteroaryl, the group is designated (5- to 10-membered heteroaryl)C₀-C₈alkyl. A (5- to 7-membered heterocycle)C₀-C₈alkyl is a 5- to 7-membered heterocyclic ring linked via a bond or a C₁-C₈alkyl group; a (4- to 7-membered heterocycle)C₀-C₈alkyl is a 4- to 7-membered heterocyclic ring linked via a bond or a C₁-C₈alkyl group.

Certain heterocyclic groups are 5- to 8-membered heterocyclic rings, optionally substituted as described above. (C₅-C₈)heterocycloalkyls include, for example, piperidinyl, piperazinyl, pyrrolidinyl, azepanyl, morpholino and thiomorpholino, as well as groups in which each of the foregoing is substituted with from 1 to 6 (preferably from 1 to 4) substituents.

A "substituent," as used herein, refers to a molecular moiety that is covalently bonded to an atom within a molecule of interest. For example, a "ring substituent" may be a moiety such as a halogen, alkyl group, haloalkyl group or other group discussed herein that is covalently bonded to an atom (preferably a carbon or nitrogen atom) that is a ring member. The term "substitution" refers to replacing a hydrogen atom in a molecular structure with a substituent as described above, such that the valence on the designated atom is not exceeded, and such that a chemically stable compound (*i.e.*, a compound that can be isolated, characterized, and tested for biological activity) results from the substitution.

Groups that are "optionally substituted" are unsubstituted or are substituted by other than hydrogen at one or more available positions, typically 1, 2, 3, 4, 5 or 6 positions, by one or more suitable groups (which may be the same or different). Such optional substituents include, for example, hydroxy, halogen, cyano, nitro, C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkyl ether, C₃-C₈alkanone, C₁-C₈alkylthio, amino, mono- or di-(C₁-C₈alkyl)amino, C₁-C₈haloalkyl, C₁-C₈haloalkoxy, C₁-C₈alkanoyl, C₁-C₈alkanoyloxy,

C₁-C₈alkoxycarbonyl,

-COOH, -CONH₂, mono- or di-(C₁-C₈alkyl)carboxamido, -SO₂NH₂, and/or mono or di(C₁-C₈alkyl)sulfonamido, as well as carbocyclic and heterocyclic groups. Optional substitution is also indicted herein by the phrase "substituted with from 0 to X substituents," where X represents the maximum number of independently chosen substituents. For example, a group that is substituted with from 0 to 3 substituents is unsubstituted or substituted with from 1 to 3 independently chosen substituents.

The terms "VR1" and "capsaicin receptor" are used interchangeably herein to refer to a type 1 vanilloid receptor. Unless otherwise specified, these terms encompass both rat and human VR1 receptors (*e.g.*, GenBank Accession Numbers AF327067, AJ277028 and NM_018727; sequences of certain human VR1 cDNAs are provided in SEQ ID NOs:1-3, and the encoded amino acid sequences shown in SEQ ID NOs:4 and 5, of U.S. Patent No. 6,482,611), as well as homologs thereof found in other species.

A "VR1 modulator," also referred to herein as a "modulator," is a compound that modulates VR1 activation and/or VR1-mediated signal transduction. VR1 modulators specifically provided herein are compounds that satisfy one or more of Formula I, Formula Ia and subformulas II-IX, or are a pharmaceutically acceptable form of such a compound. A VR1 modulator may be a VR1 agonist or antagonist. A modulator binds with "high affinity" if the K_i at VR1 is less than 1 micromolar, preferably less than 100 nanomolar, 10 nanomolar or 1 nanomolar. A representative assay for determining K_i at VR1 is provided in Example 5, herein.

A modulator is considered an "antagonist" if it detectably inhibits vanilloid ligand binding to VR1 and/or VR1-mediated signal transduction (using, for example, the representative assay provided in Example 6); in general, such an antagonist inhibits VR1 activation with a IC₅₀ value of less than 1 micromolar, preferably less than 100 nanomolar, and more preferably less than 10 nanomolar or 1 nanomolar within the assay provided in Example 6. VR1 antagonists include neutral antagonists and inverse agonists. In certain embodiments, capsaicin receptor antagonists provided herein are non-vanilloid compounds (*i.e.*, do not comprise a phenyl ring with two oxygen atoms bound to adjacent ring carbons).

An "inverse agonist" of VR1 is a compound that reduces the activity of VR1 below its basal activity level in the absence of added vanilloid ligand. Inverse agonists of VR1 may also inhibit the activity of vanilloid ligand at VR1, and/or may also inhibit binding of vanilloid ligand to VR1. The ability of a compound to inhibit the binding of vanilloid ligand to VR1 may be measured by a binding assay, such as the binding assay given in Example 5.

The basal activity of VR1, as well as the reduction in VR1 activity due to the presence of VR1 antagonist, may be determined from a calcium mobilization assay, such as the assay of Example 6.

5 A "neutral antagonist" of VR1 is a compound that inhibits the activity of vanilloid ligand at VR1, but does not significantly change the basal activity of the receptor (*i.e.*, within a calcium mobilization assay as described in Example 6 performed in the absence of vanilloid ligand, VR1 activity is reduced by no more than 10%, more preferably by no more than 5%, and even more preferably by no more than 2%; most preferably, there is no detectable reduction in activity). Neutral antagonists of VR1 may inhibit the binding of vanilloid ligand
10 to VR1.

As used herein a "capsaicin receptor agonist" or "VR1 agonist" is a compound that elevates the activity of the receptor above the basal activity level of the receptor (*i.e.*, enhances VR1 activation and/or VR1-mediated signal transduction). Capsaicin receptor agonist activity may be identified using the representative assay provided in Example 6. In
15 general, such an agonist has an EC₅₀ value of less than 1 micromolar, preferably less than 100 nanomolar, and more preferably less than 10 nanomolar within the assay provided in Example 6. In certain embodiments, capsaicin receptor agonists provided herein are non-vanilloid compounds.

A "vanilloid" is capsaicin or any capsaicin analogue that comprises a phenyl ring with
20 two oxygen atoms bound to adjacent ring carbon atoms (one of which carbon atom is located *para* to the point of attachment of a third moiety that is bound to the phenyl ring). A vanilloid is a "vanilloid ligand" if it binds to VR1 with a K_i (determined as described herein) that is no greater than 10 μM. Vanilloid ligand agonists include capsaicin, olvanil, N-arachidonoyl-dopamine and resiniferatoxin (RTX). Vanilloid ligand antagonists include
25 capsazepine and iodo-resiniferatoxin.

A "capsaicin receptor modulatory amount" is an amount that, upon administration, achieves a concentration of VR1 modulator at a capsaicin receptor that is sufficient to alter the binding of vanilloid ligand to VR1 *in vitro* (using the assay provided in Example 5) and/or VR1-mediated signal transduction (using an assay provided in Example 6). The
30 capsaicin receptor may be present, for example, in a body fluid such as blood, plasma, serum, CSF, synovial fluid, lymph, cellular interstitial fluid, tears or urine.

A "therapeutically effective amount" is an amount that, upon administration, is sufficient to provide detectable patient relief from a condition being treated. Such relief may

be detected using any appropriate criteria, including alleviation of one or more symptoms, such as pain.

A "patient" is any individual treated with a VR1 modulator as provided herein. Patients include humans, as well as other animals such as companion animals (*e.g.*, dogs and cats) and livestock. Patients may be experiencing one or more symptoms of a condition responsive to capsaicin receptor modulation (*e.g.*, pain, exposure to vanilloid ligand, itch, urinary incontinence, respiratory disorders, cough and/or hiccup), or may be free of such symptom(s) (*i.e.*, treatment may be prophylactic).

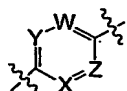
VR1 MODULATORS

As noted above, the present invention provides VR1 modulators that may be used in a variety of contexts, including in the treatment of pain (*e.g.*, neuropathic or peripheral nerve-mediated pain); exposure to capsaicin; exposure to acid, heat, light, tear gas air pollutants, pepper spray or related agents; respiratory conditions such as asthma or chronic obstructive pulmonary disease; itch; urinary incontinence; cough or hiccup; and/or obesity. VR1 modulators may also be used within *in vitro* assays (*e.g.*, assays for receptor activity), as probes for detection and localization of VR1 and as standards in ligand binding and VR1-mediated signal transduction assays.

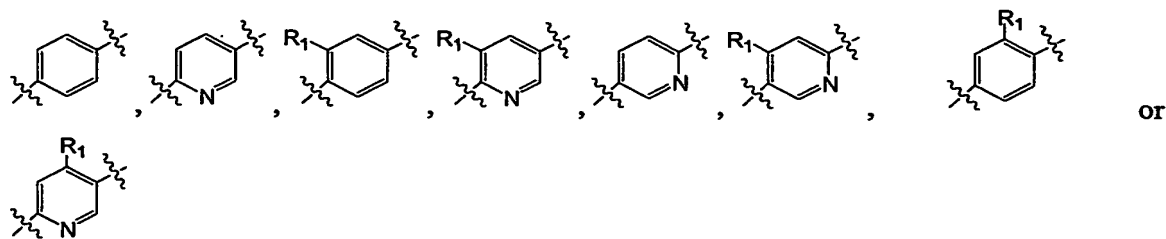
VR1 modulators provided herein are substituted biphenyl-4-carboxylic acid arylamide analogues that detectably modulate the binding of capsaicin to VR1 at nanomolar (*i.e.*, submicromolar) concentrations, preferably at subnanomolar concentrations, more preferably at concentrations below 100 picomolar, or even below 20 picomolar. Such modulators are preferably not capsaicin analogs. Certain preferred modulators are VR1 antagonists and have no detectable agonist activity in the assay described in Example 6. In certain embodiments, VR1 modulators provided herein further bind with high affinity to VR1.

The present invention is based, in part, on the discovery that small molecules having the general Formula I or Ia (as well as pharmaceutically acceptable forms thereof) modulate VR1 activity. In certain embodiments, such compounds satisfy any one or more of Formulas II-IX, above.

In certain compounds of Formulas I, Ia, or II-IX, the group designated



is an optionally substituted phenyl or pyridyl ring, such as



In certain such compounds, W, Y and Z are CR₁, with each R₁ at W, Y and Z independently chosen from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, -N(H)SO₂C₁-C₄alkyl, -N(C₁-C₄alkyl)SO₂C₁-C₄alkyl and -N(SO₂C₁-C₄alkyl)₂. For example, each R₁ at W, Y and Z may be independently selected from hydrogen, halogen, hydroxy and C₁-C₄alkyl. Within certain compounds, X is N or CH. Within other compounds, W and Z are each CH, X is N or CH, and Y is CR₁. In further such compounds, W, Y and Z are each CH, and X is N or CH.

In other such compounds, W is N and X, Y, and Z are CR₁, with each R₁ at X, Y and Z independently chosen from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, -SO₂C₁-C₈alkyl, -SO₂N(H)C₁-C₈alkyl, -SO₂N(C₁-C₈alkyl)₂, -N(H)SO₂C₁-C₄alkyl, -N(C₁-C₄alkyl)SO₂C₁-C₄alkyl and -N(SO₂C₁-C₄alkyl)₂. For example, each R₁ at X, Y and Z may be independently selected from hydrogen, halogen, hydroxy and C₁-C₄alkyl.

As noted above, the variable L in Formulas I and III-V is independently selected at

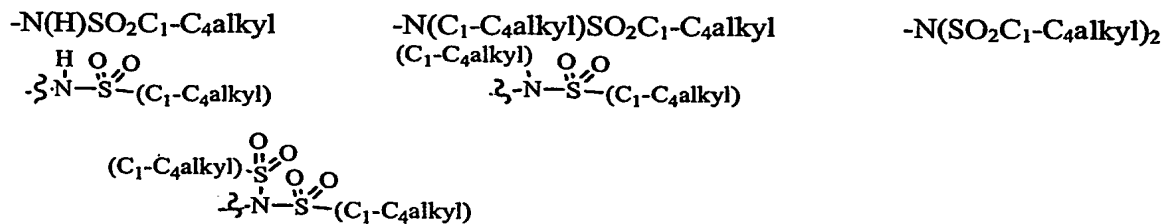
each occurrence from: a bond, O, C(=O) (*i.e.*, $\text{--}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{--}$), OC(=O) (*i.e.*, $\text{--}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{--}$), C(=O)O (*i.e.*, $\text{--}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{--}\text{O--}$), O-C(=O)O (*i.e.*, $\text{--}\text{O--}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{--}\text{O--}$), -S(O)_m (*i.e.*, -S-, $\text{--}\overset{\text{O}}{\underset{\text{||}}{\text{S}}}\text{--}$, or $\text{--}\overset{\text{O}}{\underset{\text{||}}{\text{S}}}\text{--}\overset{\text{O}}{\underset{\text{||}}{\text{S}}}\text{--}$), N(R_x) (*i.e.*, $\text{--}\overset{\text{R}_x}{\underset{|}{\text{N}}}\text{--}$), C(=O)N(R_x) (*i.e.*, $\text{--}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{--}\overset{\text{R}_x}{\underset{|}{\text{N}}}\text{--}$), N(R_x)C(=O) (*i.e.*, $\text{--}\overset{\text{R}_x}{\underset{|}{\text{N}}}\text{--}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{--}$), N(R_x)S(O)_m (*e.g.*, $\text{--}\overset{\text{R}_x}{\underset{|}{\text{N}}}\text{--}\overset{\text{O}}{\underset{\text{||}}{\text{S}}}\text{--}\overset{\text{O}}{\underset{\text{||}}{\text{S}}}\text{--}$),

S(O)_mN(R_x) (*e.g.*, $\text{--}\overset{\text{O}}{\underset{\text{||}}{\text{S}}}\text{--}\overset{\text{O}}{\underset{\text{||}}{\text{S}}}\text{--}\overset{\text{R}_x}{\underset{|}{\text{N}}}\text{--}$), and N[S(O)_mR_x]S(O)_m (*e.g.*, $\text{--}\overset{\text{R}_x}{\underset{|}{\text{N}}}\text{--}\overset{\text{O}}{\underset{\text{||}}{\text{S}}}\text{--}\overset{\text{O}}{\underset{\text{||}}{\text{S}}}\text{--}\overset{\text{O}}{\underset{\text{||}}{\text{S}}}\text{--}$), wherein m is 0, 1 or 2 and R_x is independently selected at each occurrence from hydrogen and C₁-C₈alkyl. Within

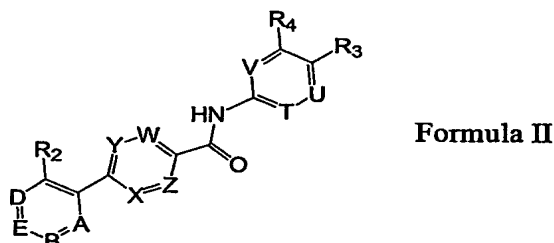
certain compounds, L is independently chosen at each occurrence from a bond, O, C(=O), S(O)_m, N(R_x), C(=O)N(R_x), N(R_x)C(=O), N(R_x)S(O)_m, S(O)_mN(R_x) and N[S(O)_mR_x]S(O)_m. Within other such compounds, L is referred to herein as L_a, and is independently chosen at each occurrence from a bond, O, C(=O), C(=O)O, O-C(=O)O, S(O)_m, N(R_x), N(R_x)C(=O), N(R_x)S(O)_m, S(O)_mN(R_x), and N[S(O)_mR_x]S(O)_m. If L is a bond, R_a or M is linked directly to

a ring atom; otherwise, L is located between a ring atom and R_a. In the structural drawings of L moieties shown above, the bond on the left side is attached to the ring atom and the bond on the right is attached to R_a. It will be apparent that hydrogen, hydroxy and amino groups are within the scope of substituents characterized by L-M, L_a-M and L_a-R_a.

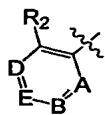
5 For clarity, the following substituents have the structures indicated below:



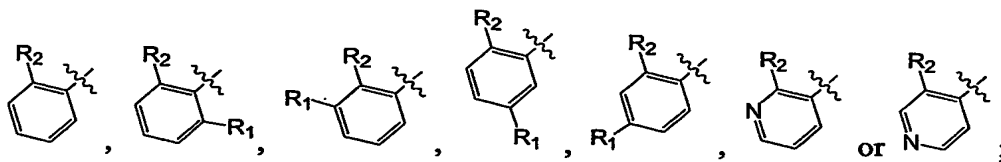
10 Certain preferred compounds provided by the invention include those compounds according to FORMULA II



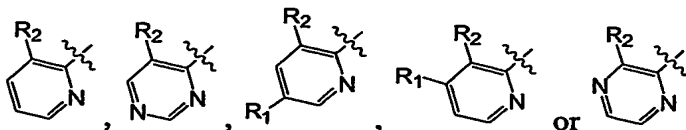
Variables in Formula II are generally as described above. In certain compounds of Formula II, the group designated:



is optionally substituted phenyl or pyridyl in which A is CR₁, such as



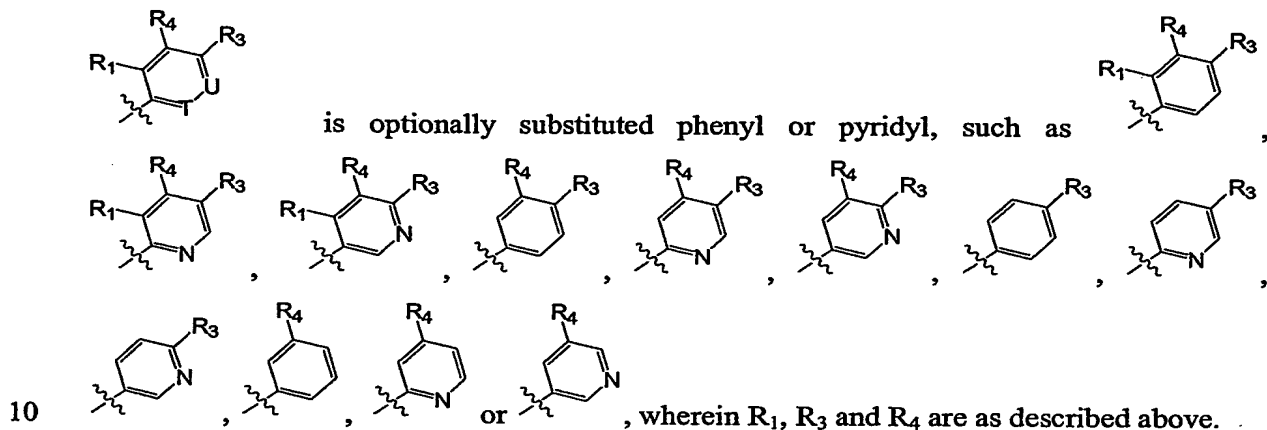
15 or optionally substituted pyridyl or pyrimidyl in which A is N, such as



In certain embodiments, B and D are CR₁, with each R₁ at B and D independently chosen from hydrogen, halogen, cyano, C₁-C₄alkyl, C₁-C₄haloalkyl and C₁-C₄alkoxy. E, in certain embodiments, is N or CR₁, wherein R₁ at E is hydrogen, C₁-C₄alkyl or C₁-C₂alkoxy; preferably R₁ at E is hydrogen. R₂ of Formula II is preferably selected from cyano, CHO, nitro, NHOH, C₁-C₄alkyl (e.g., methyl,

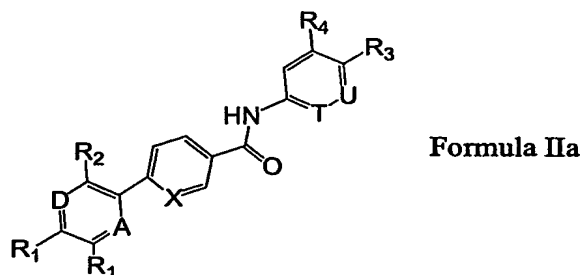
ethyl or propyl), C₁-C₄haloalkyl (e.g., trifluoromethyl or 2,2,2-trifluoroethyl), C₁-C₄alkoxy (e.g., methoxy, ethoxy or propoxy), C₁-C₄hydroxyalkyl (e.g., hydroxymethyl), C₁-C₄alkylthio (e.g., methylthio or ethylthio), C₁-C₄alkanoyl (e.g., CHO), aminoC₀-C₄alkyl, mono- and di-(C₁-C₄alkyl)aminoC₀-C₄alkyl, (C₅-C₆cycloalkylamino), (5- and 6-membered heterocycloalkyl)C₀-C₄alkyl, -N(R_x)SO₂(C₁-C₄alkyl) (e.g., -N(H)SO₂C₁-C₄alkyl or -N(CH₃)SO₂C₁-C₄alkyl) and -N(SO₂C₁-C₄alkyl)₂ (e.g., -(SO₂CH₃)₂).

Within certain compounds of Formula II, the group designated:



R₃ and R₄ of Formula II are preferably independently selected from hydrogen, halogen, C₁-C₄alkyl, C₂-C₄alkyl ether, C₁-C₄haloalkyl, C₁-C₄hydroxyalkyl and -SO₂CF₃; or are taken together to form a fused ring chosen from 5-membered carbocyclic or heterocyclic rings, phenyl and 5- to 7-membered partially saturated heterocycloalkyl rings such as dioxane or dioxepane. In certain compounds of Formula II, one of R₃ and R₄ is hydrogen and the other is selected from halogen, C₁-C₄alkyl and C₁-C₄haloalkyl. Within other compounds of Formula II, R₃ and R₄ are each independently selected from halogen, C₁-C₄alkyl and C₁-C₄haloalkyl.

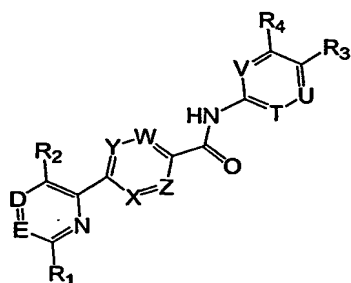
Certain compounds of Formula II further satisfy Formula IIa:



20 wherein A, D, T, U, X, R₁, R₂, R₃ and R₄ are as described for Formula II. In certain compounds of Formula IIa: A, T, U and X are independently N or CH; D is CH; each R₁ is

independently chosen from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, -N(H)SO₂C₁-C₄alkyl, -N(C₁-C₄alkyl)SO₂C₁-C₄alkyl and -N(SO₂C₁-C₄alkyl)₂; R₂ is cyano, CHO, amino, nitro, methyl, ethyl, propyl, trifluoromethyl, trifluoroethyl, methoxy, ethoxy, propoxy, methylthio, ethylthio, -N(H)SO₂C₁-C₄alkyl, -N(CH₃)SO₂C₁-C₄alkyl or -N(SO₂CH₃)₂; and R₃ and R₄ are each independently selected from hydrogen, halogen, C₁-C₄alkyl, C₂-C₄alkyl ether, C₁-C₄haloalkyl, C₁-C₄hydroxyalkyl and -SO₂CF₃; or R₃ and R₄ are taken together to form a fused ring chosen from 5-membered carbocyclic or heterocyclic rings, phenyl, dioxane and dioxepane.

Other preferred compounds provided by the invention include those compounds according to FORMULA III



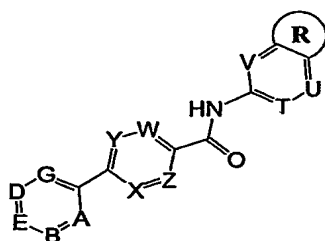
Formula III

Variables in Formula III are generally as described above. R₂ of Formula III is preferably selected from (i) halogen (*e.g.*, chloro or fluoro), nitro, cyano and -NOH; and (ii) C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, aminoC₀-C₆alkyl, mono- and di-(C₁-C₆alkyl)aminoC₀-C₆alkyl, oxadiazolyl, pyrazolyl, (5- and 6-membered heterocycloalkyl)C₀-C₆alkyl, -N(H)SO₂C₁-C₆alkyl, -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂ and N(H)SO₂-(C₁-C₆alkyl)-phenyl, each of which is substituted with from 0 to 4 substituents independently chosen from halogen, hydroxy, cyano, C₁-C₄alkyl and C₁-C₄haloalkyl. In certain such compounds, R₂ is selected from fluoro, chloro, cyano, nitro, C₁-C₄alkyl (*e.g.*, methyl, ethyl or propyl), C₁-C₄haloalkyl (*e.g.*, trifluoromethyl or 2,2,2-trifluoroethyl), C₁-C₄hydroxyalkyl, C₁-C₄alkoxy (*e.g.*, methoxy, ethoxy or propoxy), C₁-C₄alkylthio (*e.g.*, methylthio or ethylthio), C₁-C₄alkanoyl (*e.g.*, CHO), aminoC₀-C₄alkyl, mono- and di-(C₁-C₄alkyl)aminoC₀-C₄alkyl, (C₅-C₆cycloalkyl)amino, (5- and 6-membered heterocycloalkyl)C₀-C₄alkyl, -N(H)SO₂C₁-C₄alkyl, -N(C₁-C₄alkyl)SO₂C₁-C₄alkyl (*e.g.*, -N(CH₃)SO₂C₁-C₄alkyl) and -N(SO₂C₁-C₄alkyl)₂ (*e.g.*, -N(SO₂CH₃)₂).

Within certain compounds of Formula III, R₃ is selected from (a) halogen; and (b) C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, -SO₂CF₃, C₂-C₆alkyl ether and 5- to 7-membered heterocycloalkyl, each of which is substituted with from 0 to 3

substituents independently selected from hydroxy, halogen, cyano, oxo, C₁-C₄alkyl and C₁-C₄haloalkyl. Representative R₃ groups include C₁-C₆alkyl (e.g., methyl, ethyl, propyl, isopropyl, and t-butyl), C₁-C₆haloalkyl (e.g., trifluoromethyl and trifluoroethyl), C₁-C₆hydroxyalkyl (e.g., hydroxy methyl, hydroxyethyl and -C(CH₃)₂OH) and C₁-C₆cyanoalkyl (e.g., cyanomethyl, cyanoethyl and -C(CH₃)₂CN). Within other compounds of Formula III, R₃ is taken together with R₄ to form a fused ring chosen from cyclopentane, thiazole, dioxolane, dioxane and dioxepane, each of which fused ring is substituted with from 0 to 2 substituents such as methyl.

Yet other preferred compounds provided by the invention include those compounds according to FORMULA IV



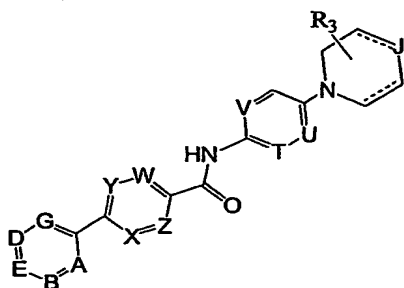
Formula IV

Variables in Formula IV are generally as described above. Within certain compounds of Formula IV, at least two of W, X, Y and Z are CR₁, and at least one of T and U is CH or CR₈. R₁, in certain compounds of Formula IV, is independently chosen from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl and C₁-C₄alkoxy. Within one subclass of such compounds, each R₁ is hydrogen and X is N or CH.

Certain compounds of Formula IV contain at least one ring nitrogen atom; for example, X may be N and/or A may be N. G, in one subclass of Formula IV compounds, is CR₇. In certain such compounds, B, D and E are CH or CR₇; A in one subclass of such compounds is N or CH. In further such compounds, R₇ at the G position is cyano, fluoro, chloro, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄hydroxyalkyl, C₁-C₄alkoxy, C₁-C₄alkylthio, C₁-C₄alkanoyl, aminoC₀-C₄alkyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), (C₅-C₆cycloalkyl)amino, (5- or 6-membered heterocycloalkyl)C₀-C₄alkyl, -N(H)SO₂C₁-C₄alkyl, -N(H)SO₂-(C₀-C₂alkyl)-phenyl, -N(C₁-C₄alkyl)(SO₂C₁-C₄alkyl) or -N(SO₂C₁-C₄alkyl)₂. In other compounds of Formula IV, R₇ at all positions where this variable occurs is independently selected from halogen, amino, cyano, nitro, CHO, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, C₁-C₄alkylthio, -N(H)SO₂C₁-C₄alkyl, -N(CH₃)SO₂C₁-C₄alkyl and -N(SO₂CH₃)₂.

The group designated **R** in Formula IV represents a fused 5- or 7-membered ring or a fused dioxane ring and, in certain compounds, is substituted with from 0 to 2 substituents independently selected from oxo, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy and C₁-C₄haloalkoxy. In certain embodiments, the fused ring is chosen from cyclopentene, cyclopentene substituted with 1 or 2 oxo, thiazole, or methylthiazole; in other embodiments, the fused ring is chosen from dioxolane, dioxane and dioxepane.

Certain other preferred compounds provided by the invention include those compounds according to FORMULA V



Formula V

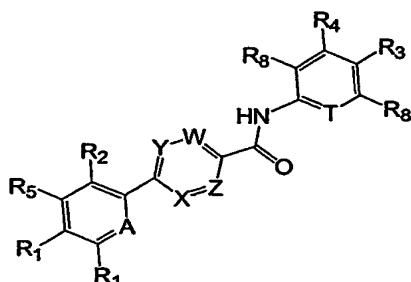
10 Variables in Formula V are generally as described above. Within certain compounds of Formula V, at least two of W, X, Y and Z are CR₁, and at least one of T and U is CR₈. Each R₁ and R₈, in certain compounds of Formula V, is independently chosen from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl and C₁-C₄alkoxy.

Certain compounds of Formula V contain at least one ring nitrogen atom; for example, X may be N and/or A may be N. In certain embodiments, A is N or CH. G, in one subclass of Formula V compounds, is CR₇. In certain such compounds, R₇ at the G position is cyano, fluoro, chloro, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄hydroxyalkyl, C₁-C₄alkoxy, C₁-C₄alkylthio, C₁-C₄alkanoyl, aminoC₀-C₄alkyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), (C₅-C₆cycloalkyl)amino, (5- or 6-membered heterocycloalkyl)C₀-C₄alkyl, -N(H)SO₂C₁-C₄alkyl, -N(C₁-C₄alkyl)SO₂C₁-C₄alkyl or -N(SO₂C₁-C₄alkyl)₂. In other compounds of Formula V, R₇ at all positions where this variable occurs is independently selected from halogen, amino, cyano, nitro, CHO, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, C₁-C₄alkylthio, -N(H)SO₂C₁-C₄alkyl, -N(CH₃)SO₂C₁-C₄alkyl and -N(SO₂CH₃)₂.

25 Within certain compounds of Formula V, R₉ represents from 0 to 2 substituents independently chosen from halogen, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₄haloalkyl and C₁-C₄haloalkoxy. J is preferably O, with each bond shown as --- a single bond. In one subclass of such compounds, J is O; each R₇ is independently selected from halogen, amino,

cyano, nitro, CHO, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, C₁-C₄alkylthio, -N(H)SO₂(C₁-C₄alkyl), -N(CH₃)SO₂(C₁-C₄alkyl) and -N(SO₂CH₃)₂; R₁ at W, Y and Z is CR₁, wherein each R₁ is independently chosen from hydrogen, halogen, hydroxy and C₁-C₄alkyl; A is N or CH; and T and U are independently N or CH.

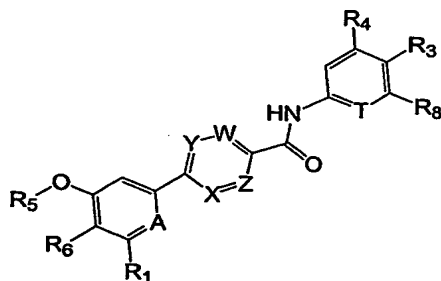
- 5 Certain preferred compounds provided by the invention include those compounds according to FORMULA VI



Formula VI

- Variables in Formula VI are generally as described above. Within certain compounds of Formula VI, A and T are independently CH or N. Each R₁ and R₈, in certain compounds of Formula VI, is independently chosen from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl and C₁-C₄alkoxy. Within further compounds of Formula VI, at least two of W, X, Y and Z are CR₁. For example, in certain compounds, W and X are CH. In one subclass of Formula VI, each R₁ is hydrogen or halogen and each R₈ is hydrogen. Within one subclass of Formula VI, W and X are CH, A and T are independently CH or N, each R₁ is hydrogen or halogen, and each R₈ is hydrogen. In other such compounds, R₃ is C₁-C₆alkyl and R₄ is hydrogen, methyl or halogen. In still further such compounds, R₃ is hydrogen or halogen and R₄ is halogen.

Yet other preferred compounds provided by the invention include those compounds according to FORMULA VII

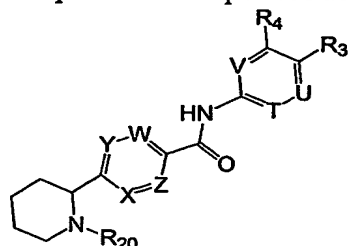


Formula VII

- Variables in Formula VII are generally as described above. Within certain compounds of Formula VII, R₃ and R₄ are taken together to form a fused cyclopentene, thiazole, dioxane or dioxolane ring, each of which is unsubstituted or substituted with a methyl group. Within further compounds of Formula VII, at least two of W, X, Y and Z are

CR₁. Each R₁ and R₈, in certain compounds of Formula VII, is independently chosen from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl and C₁-C₄alkoxy. In one subclass of such compounds, each R₁ and R₈ is hydrogen.

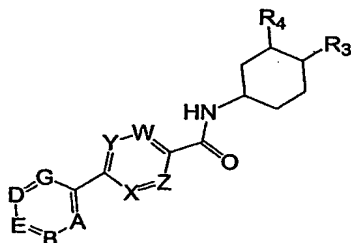
The invention further provides compounds according to FORMULA VIII



Formula VIII

5 Variables in Formula VIII are generally as described above. Within certain compounds of Formula VIII, the variables W, X, Y and Z are each CH. Within further compounds, V, U and T are each CH. R₄, in certain embodiments, is hydrogen; and R₃, in certain embodiments, is C₁-C₄alkyl, trifluoromethyl, cyano or halogen.

10 Certain preferred compounds provided by the invention include those compounds according to FORMULA IX



Formula IX

15 Variables in Formula IX are generally as described above. Within certain compounds of Formula IX, the variables W, X, Y and Z are each CH. Within further compounds, V, U and T are each CH. R₄, in certain embodiments, is hydrogen; and R₃, in certain embodiments, is C₁-C₄alkyl, trifluoromethyl, cyano or halogen. In certain compounds, A is N; B, E and D are each CH; and G is CR₁, with R₁ chosen from halogen, C₁-C₄alkyl, trifluoromethyl or cyano.

20 Certain representative biphenyl-4-carboxylic acid arylamide analogues are provided in Examples 1-3. It will be apparent that the specific compounds recited therein are representative only, and are not intended to limit the scope of the present invention. Further, as noted above, all compounds of the present invention may be present as a pharmaceutically acceptable form, such as a hydrate or acid addition salt.

Substituted biphenyl-4-carboxylic acid arylamide analogues provided herein detectably alter (modulate) VR1 activity, as determined using a standard *in vitro* VR1 ligand binding assay and/or a functional assay such as a calcium mobilization assay, dorsal root ganglion assay or *in vivo* pain relief assay. References herein to a "VR1 ligand binding assay" are intended to refer to a standard *in vitro* receptor binding assay such as that provided in Example 5, and a "calcium mobilization assay" (also referred to herein as a "signal transduction assay") may be performed as described in Example 6. Briefly, to assess binding to VR1, a competition assay may be performed in which a VR1 preparation is incubated with labeled (*e.g.*, ^{125}I or ^3H) compound that binds to VR1 (*e.g.*, a capsaicin receptor agonist such as RTX) and unlabeled test compound. Within the assays provided herein, the VR1 used is preferably a mammalian VR1, more preferably a human or rat VR1. The receptor may be recombinantly expressed or naturally expressed. The VR1 preparation may be, for example, a membrane preparation from HEK293 or CHO cells that recombinantly express human VR1. Incubation with a compound that detectably modulates vanilloid ligand binding to VR1 will result in a decrease or increase in the amount of label bound to the VR1 preparation, relative to the amount of label bound in the absence of the compound. This decrease or increase may be used to determine the K_i at VR1 as described herein. In certain aspects, compounds that decrease the amount of label bound to the VR1 preparation within such an assay are preferred.

As noted above, compounds that are VR1 antagonists are preferred within certain embodiments. IC_{50} values for such compounds may be determined using a standard *in vitro* VR1-mediated calcium mobilization assay, as provided in Example 6. Briefly, cells expressing capsaicin receptor are contacted with a compound of interest and with an indicator of intracellular calcium concentration (*e.g.*, a membrane permeable calcium sensitivity dye such as Fluo-3 or Fura-2 (both of which are available, for example, from Molecular Probes, Eugene, OR), each of which produce a fluorescent signal when bound to Ca^{++}). Such contact is preferably carried out by one or more incubations of the cells in buffer or culture medium comprising either or both of the compound and the indicator in solution. Contact is maintained for an amount of time sufficient to allow the dye to enter the cells (*e.g.*, 1-2 hours). Cells are washed or filtered to remove excess dye and are then contacted with a vanilloid receptor agonist (*e.g.*, capsaicin, RTX or olvanil), typically at a concentration equal to the EC_{50} concentration, and a fluorescence response is measured. When cells are contacted with a compound that is a VR1 antagonist, and with a vanilloid receptor agonist, the fluorescence response is generally reduced by at least 20%, preferably at least 50% and more.

preferably at least 80%, as compared to cells that are contacted with the agonist in the absence of test compound. The IC_{50} for VR1 antagonists provided herein is preferably less than 1 micromolar, less than 100 nM, less than 10 nM or less than 1 nM. In other embodiments, compounds that are capsaicin receptor agonists are preferred. Capsaicin receptor agonist activity may generally be determined as described in Example 6. When cells are contacted with 1 micromolar of a compound that is a VR1 agonist, the fluorescence response is generally increased by an amount that is at least 30% of the increase observed when cells are contacted with 100 nM capsaicin. The EC_{50} for VR1 agonists provided herein is preferably less than 1 micromolar, less than 100 nM or less than 10 nM.

VR1 modulating activity may also, or alternatively, be assessed using a cultured dorsal root ganglion assay as provided in Example 9 and/or an *in vivo* pain relief assay as provided in Example 10. Compounds provided herein preferably have a statistically significant specific effect on VR1 activity within one or more functional assays provided herein.

Within certain embodiments, VR1 modulators provided herein do not substantially modulate ligand binding to other cell surface receptors, such as EGF receptor tyrosine kinase or the nicotinic acetylcholine receptor. In other words, such modulators do not substantially inhibit activity of a cell surface receptor such as the human epidermal growth factor (EGF) receptor tyrosine kinase or the nicotinic acetylcholine receptor (*e.g.*, the IC_{50} or IC_{40} at such a receptor is preferably greater than 1 micromolar, and most preferably greater than 10 micromolar). Preferably, a modulator does not detectably inhibit EGF receptor activity or nicotinic acetylcholine receptor activity at a concentration of 0.5 micromolar, 1 micromolar or more preferably 10 micromolar. Assays for determining cell surface receptor activity are commercially available, and include the tyrosine kinase assay kits available from Panvera (Madison, WI).

Preferred VR1 modulators provided herein are non-sedating. In other words, a dose of VR1 modulator that is twice the minimum dose sufficient to provide analgesia in an animal model for determining pain relief (such as a model provided in Example 10, herein) causes only transient (*i.e.*, lasting for no more than $\frac{1}{2}$ the time that pain relief lasts) or preferably no statistically significant sedation in an animal model assay of sedation (using the method described by Fitzgerald et al. (1988) *Toxicology* 49(2-3):433-9). Preferably, a dose that is five times the minimum dose sufficient to provide analgesia does not produce statistically significant sedation. More preferably, a VR1 modulator provided herein does not produce sedation at intravenous doses of less than 25 mg/kg (preferably less than 10 mg/kg)

or at oral doses of less than 140 mg/kg (preferably less than 50 mg/kg, more preferably less than 30 mg/kg).

If desired, VR1 modulators provided herein may be evaluated for certain pharmacological properties including, but not limited to, oral bioavailability (preferred compounds are orally bioavailable to an extent allowing for therapeutically effective concentrations of the compound to be achieved at oral doses of less than 140 mg/kg, preferably less than 50 mg/kg, more preferably less than 30 mg/kg, even more preferably less than 10 mg/kg, still more preferably less than 1 mg/kg and most preferably less than 0.1 mg/kg), toxicity (a preferred VR1 modulator is nontoxic when a capsaicin receptor modulatory amount is administered to a subject), side effects (a preferred VR1 modulator produces side effects comparable to placebo when a therapeutically effective amount of the compound is administered to a subject), serum protein binding and *in vitro* and *in vivo* half-life (a preferred VR1 modulator exhibits an *in vitro* half-life that is equal to an *in vivo* half-life allowing for Q.I.D. dosing, preferably T.I.D. dosing, more preferably B.I.D. dosing, and most preferably once-a-day dosing). In addition, differential penetration of the blood brain barrier may be desirable for VR1 modulators used to treat pain by modulating CNS VR1 activity such that total daily oral doses as described above provide such modulation to a therapeutically effective extent, while low brain levels of VR1 modulators used to treat peripheral nerve mediated pain may be preferred (*i.e.*, such doses do not provide brain (*e.g.*, CSF) levels of the compound sufficient to significantly modulate VR1 activity). Routine assays that are well known in the art may be used to assess these properties, and identify superior compounds for a particular use. For example, assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound (*e.g.*, intravenously). Serum protein binding may be predicted from albumin binding assays. Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described within Example 7, herein.

As noted above, preferred VR1 modulators provided herein are nontoxic. In general, the term "nontoxic" as used herein shall be understood in a relative sense and is intended to refer to any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to mammals (preferably humans) or, in keeping with established criteria, is susceptible to approval by the FDA for administration to

mammals (preferably humans). In addition, a highly preferred nontoxic compound generally satisfies one or more of the following criteria: (1) does not substantially inhibit cellular ATP production; (2) does not significantly prolong heart QT intervals; (3) does not cause substantial liver enlargement, and (4) does not cause substantial release of liver enzymes.

5 As used herein, a VR1 modulator that "does not substantially inhibit cellular ATP production" is a compound that satisfies the criteria set forth in Example 8, herein. In other words, cells treated as described in Example 8 with 100 μ M of such a compound exhibit ATP levels that are at least 50% of the ATP levels detected in untreated cells. In more highly preferred embodiments, such cells exhibit ATP levels that are at least 80% of the ATP levels
10 detected in untreated cells.

 A VR1 modulator that "does not significantly prolong heart QT intervals" is a compound that does not result in a statistically significant prolongation of heart QT intervals (as determined by electrocardiography) in guinea pigs, minipigs or dogs upon administration of twice the minimum dose yielding a therapeutically effective *in vivo* concentration. In
15 certain preferred embodiments, a dose of 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally does not result in a statistically significant prolongation of heart QT intervals. By "statistically significant" is meant results varying from control at the $p < 0.1$ level or more preferably at the $p < 0.05$ level of significance as measured using a standard parametric assay of statistical significance such as a student's T test.

20 A VR1 modulator "does not cause substantial liver enlargement" if daily treatment of laboratory rodents (*e.g.*, mice or rats) for 5-10 days with twice the minimum dose that yields a therapeutically effective *in vivo* concentration results in an increase in liver to body weight ratio that is no more than 100% over matched controls. In more highly preferred
25 embodiments, such doses do not cause liver enlargement of more than 75% or 50% over matched controls. If non-rodent mammals (*e.g.*, dogs) are used, such doses should not result in an increase of liver to body weight ratio of more than 50%, preferably not more than 25%, and more preferably not more than 10% over matched untreated controls. Preferred doses within such assays include 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally.

30 Similarly, a VR1 modulator "does not promote substantial release of liver enzymes" if administration of twice the minimum dose yielding a therapeutically effective *in vivo* concentration does not elevate serum levels of ALT, LDH or AST in laboratory rodents by more than 100% over matched mock-treated controls. In more highly preferred
 embodiments, such doses do not elevate such serum levels by more than 75% or 50% over

matched controls. Alternatively, a VR1 modulator "does not promote substantial release of liver enzymes" if, in an *in vitro* hepatocyte assay, concentrations (in culture media or other such solutions that are contacted and incubated with hepatocytes *in vitro*) equivalent to two-fold the minimum *in vivo* therapeutic concentration of the compound do not cause detectable release of any of such liver enzymes into culture medium above baseline levels seen in media from matched mock-treated control cells. In more highly preferred embodiments, there is no detectable release of any of such liver enzymes into culture medium above baseline levels when such compound concentrations are five-fold, and preferably ten-fold the minimum *in vivo* therapeutic concentration of the compound.

10 In other embodiments, certain preferred VR1 modulators do not inhibit or induce microsomal cytochrome P450 enzyme activities, such as CYP1A2 activity, CYP2A6 activity, CYP2C9 activity, CYP2C19 activity, CYP2D6 activity, CYP2E1 activity or CYP3A4 activity at a concentration equal to the minimum therapeutically effective *in vivo* concentration.

15 Certain preferred VR1 modulators are not clastogenic (*e.g.*, as determined using a mouse erythrocyte precursor cell micronucleus assay, an Ames micronucleus assay, a spiral micronucleus assay or the like) at a concentration equal to the minimum therapeutically effective *in vivo* concentration. In other embodiments, certain preferred VR1 modulators do not induce sister chromatid exchange (*e.g.*, in Chinese hamster ovary cells) at such concentrations.

20 For detection purposes, as discussed in more detail below, VR1 modulators provided herein may be isotopically-labeled or radiolabeled. For example, compounds recited in Formula I may have one or more atoms replaced by an atom of the same element having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be present in the compounds provided herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl . In addition, substitution with heavy isotopes such as deuterium (*i.e.*, ^2H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

PREPARATION OF VR1 MODULATORS

Substituted biphenyl-4-carboxylic acid arylamide analogues may generally be prepared using standard synthetic methods. In general, starting materials are commercially

available from suppliers such as Sigma-Aldrich Corp. (St. Louis, MO), or may be synthesized from commercially available precursors using established protocols. By way of example, a synthetic route similar to that shown in any of Schemes 1-5 may be used, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Each variable in the following Schemes refers to any group consistent with the description of the compounds provided herein.

In the Schemes that follow, the term "catalyst" refers to a suitable transition metal catalyst such as, but not limited to, tetrakis(triphenylphosphine)palladium(0) or palladium(II) acetate. In addition, the catalytic systems may include ligands such as, but not limited to, 2-(dicyclohexylphosphino)biphenyl and tri-*tert*-butylphosphine, and may also include a base such as K_3PO_4 , Na_2CO_3 or sodium or potassium *tert*-butoxide. Transition metal-catalyzed reactions can be carried out at ambient or elevated temperatures using various inert solvents including, but not limited to, toluene, dioxane, DMF, N-methylpyrrolidinone, ethyleneglycol dimethyl ether, diglyme and acetonitrile. When used in conjunction with suitable metal-aryl reagents, transition metal-catalyzed (hetero)aryl-aryl coupling reactions can be used, for example, to prepare the compounds encompassed in general structures 1C, 2B, 2E, 3C, 4B, and 5B. Commonly employed reagent/catalyst pairs include aryl boronic acid/palladium(0) (Suzuki reaction; Miyaura and Suzuki (1995) *Chemical Reviews* 95:2457) and aryl trialkylstannane/palladium(0) (Stille reaction; T. N. Mitchell, (1992) *Synthesis* 9:803-815), arylzinc/palladium(0) and aryl Grignard/nickel(II).

The term "activate" refers to a synthetic transformation in which a carboxylic acid moiety is converted to a suitable reactive carbonyl group, for example, an acid chloride or a mixed anhydride. These reactive carbonyl functionalities can then be reacted with the appropriate aryl-amine nucleophiles to form the corresponding aryl amide compounds as shown in the Schemes 1-5. Reagents used to activate and subsequently couple amine nucleophiles to carboxylic acids are well known to those skilled in the art of organic synthesis and include, but are not limited to, $POCl_3$, $SOCl_2$, oxalyl chloride, BOP reagent, DCC, and EDCI. These can be used, for example, to prepare compounds of general structure 1E, 2C and 2D, 3E, 4E, 4I, and 5B.

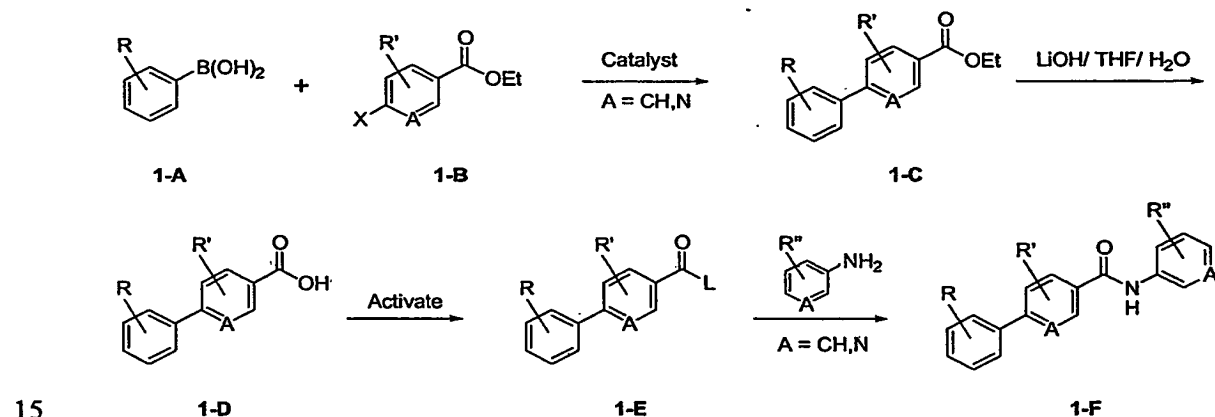
The term "reduce" refers to the process of reducing a nitro functionality to an amino functionality. This transformation can be carried out in a number of ways well known to those skilled in the art of organic synthesis including, but not limited to, catalytic hydrogenation, reduction with $SnCl_2$ and reduction with titanium trichloride. For an

overview of reduction methods see: Hudlicky, M. *Reductions in Organic Chemistry*, ACS Monograph 188, 1996.

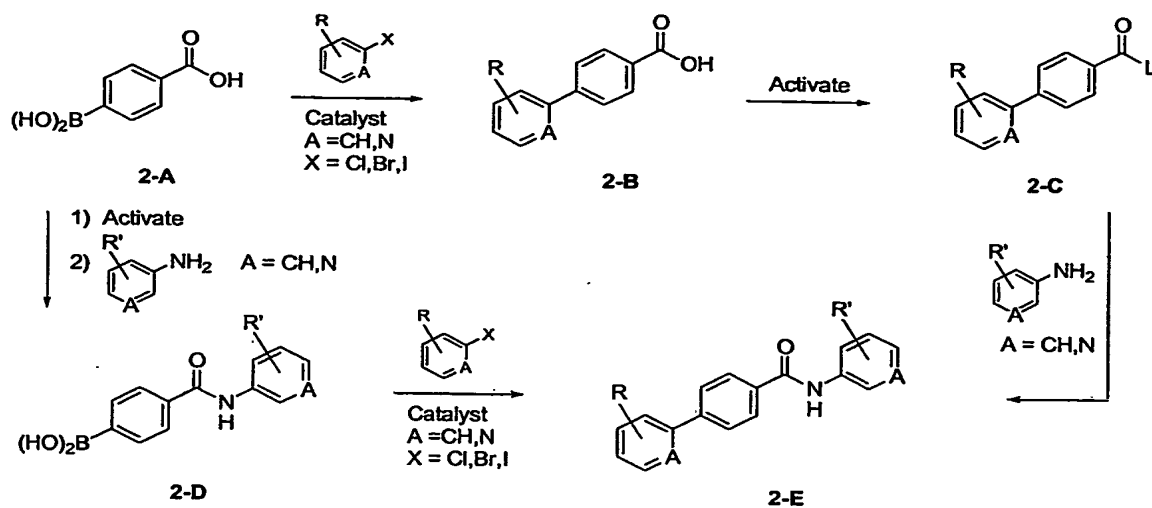
The term "oxidize" refers to a synthetic transformation wherein a methyl group is converted to a carboxylic acid functionality. Such a transformation can be used to prepare compounds such as 4D. Various reagents familiar to those skilled in the art of organic synthesis may be used to carry out this transformation including, but not limited to, KMnO_4 in basic media (*e.g.*, NaOH solution or aqueous pyridine) and $\text{K}_2\text{Cr}_2\text{O}_7$ in acidic media (*e.g.*, H_2SO_4).

The term "hydrolyze" refers to the conversion of a nitrile or ester functionality to an acid functionality by reaction with water. The reaction with water can be catalyzed by a variety of acids or bases well known to those skilled in the art of organic synthesis. This process is exemplified by the conversion of 1C to 1D and 3C to 3D.

Scheme 1

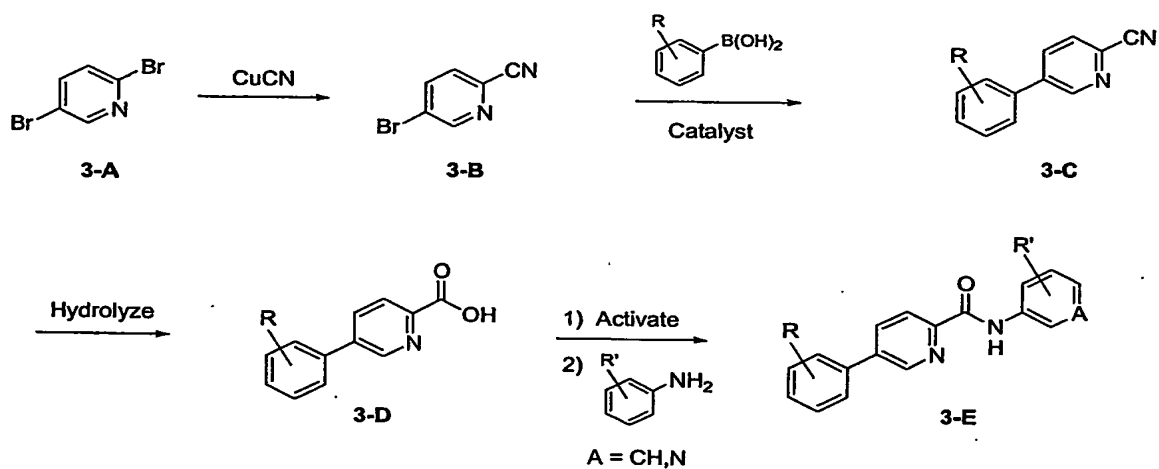


Scheme 2



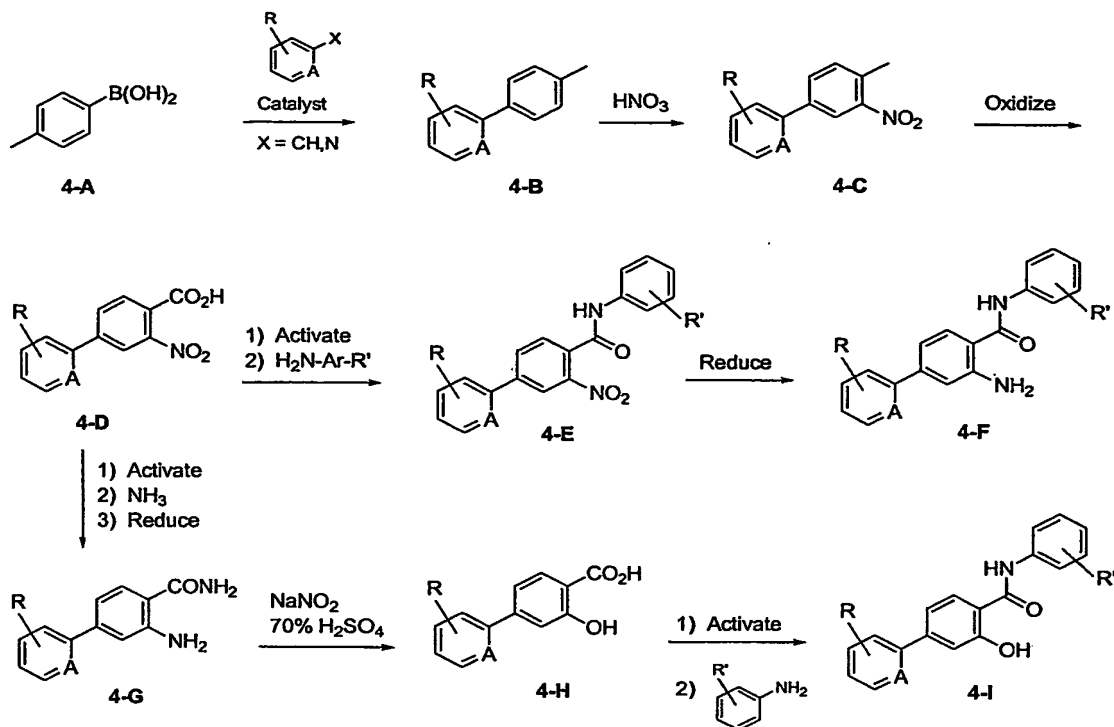
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Scheme 3



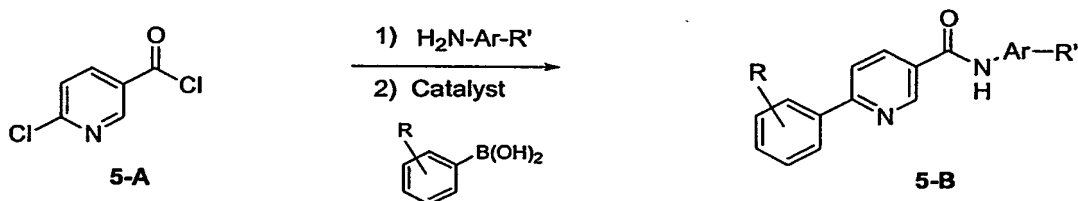
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Scheme 4



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Scheme 5



In certain embodiments, a VR1 modulator may contain one or more asymmetric carbon atoms, so that the compound can exist in different stereoisomeric forms. Such forms can be, for example, racemates or optically active forms. As noted above, all stereoisomers are encompassed by the present invention. Nonetheless, it may be desirable to obtain single enantiomers (*i.e.*, optically active forms). Standard methods for preparing single enantiomers include asymmetric synthesis and resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography using, for example a chiral HPLC column.

Compounds may be radiolabeled by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. Each radioisotope is preferably carbon (*e.g.*, ^{14}C), hydrogen (*e.g.*, ^3H), sulfur (*e.g.*, ^{35}S), or iodine (*e.g.*, ^{125}I). Tritium labeled compounds may also be prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas using the compound as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate. Preparation of radiolabeled compounds may be conveniently performed by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds.

PHARMACEUTICAL COMPOSITIONS

The present invention also provides pharmaceutical compositions comprising one or more VR1 modulators, together with at least one physiologically acceptable carrier or excipient. Pharmaceutical compositions may comprise, for example, one or more of water, buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), ethanol, mineral oil, vegetable oil, dimethylsulfoxide, carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, adjuvants, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione and/or preservatives. In addition, other active ingredients may (but need not) be included in the pharmaceutical compositions provided herein.

Pharmaceutical compositions may be formulated for any appropriate manner of administration, including, for example, topical, oral, nasal, rectal or parenteral administration. The term parenteral as used herein includes subcutaneous, intradermal, intravascular (*e.g.*, intravenous), intramuscular, spinal, intracranial, intrathecal and intraperitoneal injection, as well as any similar injection or infusion technique. In certain embodiments, compositions suitable for oral use are preferred. Such compositions include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Within yet other embodiments, compositions of the present invention may be formulated as a lyophilizate. Formulation for topical administration may be preferred for certain conditions (*e.g.*, in the treatment of skin conditions such as burns or itch). Formulation for direct administration into the bladder (intravesicular administration) may be preferred for treatment of urinary incontinence.

Compositions intended for oral use may further comprise one or more components such as sweetening agents, flavoring agents, coloring agents and/or preserving agents in order to provide appealing and palatable preparations. Tablets contain the active ingredient in admixture with physiologically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example, inert diluents (*e.g.*, calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate), granulating and disintegrating agents (*e.g.*, corn starch or alginic acid), binding agents (*e.g.*, starch, gelatin or acacia) and lubricating agents (*e.g.*, magnesium stearate, stearic acid or talc). The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (*e.g.*, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium (*e.g.*, peanut oil, liquid paraffin or olive oil).

Aqueous suspensions contain the active material(s) in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include suspending agents (*e.g.*, sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone; gum tragacanth and gum acacia); and dispersing or wetting agents (*e.g.*, naturally-occurring phosphatides such as lecithin, condensation products of an alkylene oxide with fatty acids such as polyoxyethylene stearate, condensation products of ethylene oxide with long chain aliphatic alcohols such as heptadecaethyleneoxycetanol, condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides such as polyethylene sorbitan monooleate). Aqueous suspensions may also comprise one or more preservatives, for example ethyl, or *n*-propyl *p*-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient(s) in a vegetable oil (*e.g.*, arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and/or flavoring

agents may be added to provide palatable oral preparations. Such suspensions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions may also be formulated as oil-in-water emulsions. The oily phase may be a vegetable oil (*e.g.*, olive oil or arachis oil), a mineral oil (*e.g.*, liquid paraffin) or a mixture thereof. Suitable emulsifying agents include naturally-occurring gums (*e.g.*, gum acacia or gum tragacanth), naturally-occurring phosphatides (*e.g.*, soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol), anhydrides (*e.g.*, sorbitan monoleate) and condensation products of partial esters derived from fatty acids and hexitol with ethylene oxide (*e.g.*, polyoxyethylene sorbitan monoleate). An emulsion may also comprise one or more sweetening and/or flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also comprise one or more demulcents, preservatives, flavoring agents and/or coloring agents.

Formulations for topical administration typically comprise a topical vehicle combined with active agent(s), with or without additional optional components. Suitable topical vehicles and additional components are well known in the art, and it will be apparent that the choice of a vehicle will depend on the particular physical form and mode of delivery. Topical vehicles include water; organic solvents such as alcohols (*e.g.*, ethanol or isopropyl alcohol) or glycerin; glycols (*e.g.*, butylene, isoprene or propylene glycol); aliphatic alcohols (*e.g.*, lanolin); mixtures of water and organic solvents and mixtures of organic solvents such as alcohol and glycerin; lipid-based materials such as fatty acids, acylglycerols (including oils, such as mineral oil, and fats of natural or synthetic origin), phosphoglycerides, sphingolipids and waxes; protein-based materials such as collagen and gelatin; silicone-based materials (both non-volatile and volatile); and hydrocarbon-based materials such as microsponges and polymer matrices. A composition may further include one or more components adapted to improve the stability or effectiveness of the applied formulation, such as stabilizing agents, suspending agents, emulsifying agents, viscosity adjusters, gelling agents, preservatives, antioxidants, skin penetration enhancers, moisturizers and sustained

release materials. Examples of such components are described in Martindale--The Extra Pharmacopoeia (Pharmaceutical Press, London 1993) and Martin (ed.), Remington's Pharmaceutical Sciences. Formulations may comprise microcapsules, such as hydroxymethylcellulose or gelatin-microcapsules, liposomes, albumin microspheres, microemulsions, nanoparticles or nanocapsules.

A topical formulation may be prepared in a variety of physical forms including, for example, solids, pastes, creams, foams, lotions, gels, powders, aqueous liquids and emulsions. The physical appearance and viscosity of such pharmaceutically acceptable forms can be governed by the presence and amount of emulsifier(s) and viscosity adjuster(s) present in the formulation. Solids are generally firm and non-pourable and commonly are formulated as bars or sticks, or in particulate form; solids can be opaque or transparent, and optionally can contain solvents, emulsifiers, moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product. Creams and lotions are often similar to one another, differing mainly in their viscosity; both lotions and creams may be opaque, translucent or clear and often contain emulsifiers, solvents, and viscosity adjusting agents, as well as moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product. Gels can be prepared with a range of viscosities, from thick or high viscosity to thin or low viscosity. These formulations, like those of lotions and creams, may also contain solvents, emulsifiers, moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product. Liquids are thinner than creams, lotions, or gels and often do not contain emulsifiers. Liquid topical products often contain solvents, emulsifiers, moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product.

Suitable emulsifiers for use in topical formulations include, but are not limited to, ionic emulsifiers, cetearyl alcohol, non-ionic emulsifiers like polyoxyethylene oleyl ether, PEG-40 stearate, cetareth-12, cetareth-20, cetareth-30, cetareth alcohol, PEG-100 stearate and glyceryl stearate. Suitable viscosity adjusting agents include, but are not limited to, protective colloids or non-ionic gums such as hydroxyethylcellulose, xanthan gum, magnesium aluminum silicate, silica, microcrystalline wax, beeswax, paraffin, and cetyl palmitate. A gel composition may be formed by the addition of a gelling agent such as chitosan, methyl cellulose, ethyl cellulose, polyvinyl alcohol, polyquaterniums, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carbomer or

ammoniated glycyrrhizinate. Suitable surfactants include, but are not limited to, nonionic, amphoteric, ionic and anionic surfactants. For example, one or more of dimethicone copolyol, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, lauramide DEA, cocamide DEA, and cocamide MEA, oleyl betaine, cocamidopropyl phosphatidyl PG-dimonium chloride, and ammonium laureth sulfate may be used within topical formulations. Suitable preservatives include, but are not limited to, antimicrobials such as methylparaben, propylparaben, sorbic acid, benzoic acid, and formaldehyde, as well as physical stabilizers and antioxidants such as vitamin E, sodium ascorbate/ascorbic acid and propyl gallate. Suitable moisturizers include, but are not limited to, lactic acid and other hydroxy acids and their salts, glycerin, propylene glycol, and butylene glycol. Suitable emollients include lanolin alcohol, lanolin, lanolin derivatives, cholesterol, petrolatum, isostearyl neopentanoate and mineral oils. Suitable fragrances and colors include, but are not limited to, FD&C Red No. 40 and FD&C Yellow No. 5. Other suitable additional ingredients that may be included a topical formulation include, but are not limited to, abrasives, absorbents, anti-caking agents, anti-foaming agents, anti-static agents, astringents (e.g., witch hazel, alcohol and herbal extracts such as chamomile extract), binders/excipients, buffering agents, chelating agents, film forming agents, conditioning agents, propellants, opacifying agents, pH adjusters and protectants.

An example of a suitable topical vehicle for formulation of a gel is: hydroxypropylcellulose (2.1%); 70/30 isopropyl alcohol/water (90.9%); propylene glycol (5.1%); and Polysorbate 80 (1.9%). An example of a suitable topical vehicle for formulation as a foam is: cetyl alcohol (1.1%); stearyl alcohol (0.5%); Quaternium 52 (1.0%); propylene glycol (2.0%); Ethanol 95 PGF3 (61.05%); deionized water (30.05%); P75 hydrocarbon propellant (4.30%). All percents are by weight.

Typical modes of delivery for topical compositions include application using the fingers; application using a physical applicator such as a cloth, tissue, swab, stick or brush; spraying (including mist, aerosol or foam spraying); dropper application; sprinkling; soaking; and rinsing. Controlled release vehicles can also be used.

A pharmaceutical composition may be prepared as a sterile injectible aqueous or oleaginous suspension. The modulator, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Such a composition may be formulated according to the known art using suitable dispersing, wetting agents and/or suspending agents such as those mentioned above. Among the acceptable vehicles and solvents that may be employed are water, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution.

In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectible compositions, and adjuvants such as local anesthetics, preservatives and/or buffering agents can be dissolved in the vehicle.

Modulators may also be formulated as suppositories (*e.g.*, for rectal administration). Such compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Pharmaceutical compositions may be formulated as sustained release formulations (*i.e.*, a formulation such as a capsule that effects a slow release of modulator following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of modulator release. The amount of modulator contained within a sustained release formulation depends upon, for example, the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

In addition to or together with the above modes of administration, a modulator may be conveniently added to food or drinking water (*e.g.*, for administration to non-human animals including companion animals (such as dogs and cats) and livestock). Animal feed and drinking water compositions may be formulated so that the animal takes in an appropriate quantity of the composition along with its diet. It may also be convenient to present the composition as a premix for addition to feed or drinking water.

Modulators are generally administered in a capsaicin receptor modulatory amount, and preferably a therapeutically effective amount. Preferred systemic doses are no higher than 50 mg per kilogram of body weight per day (*e.g.*, ranging from about 0.001 mg to about 50 mg per kilogram of body weight per day), with oral doses generally being about 5-20 fold higher than intravenous doses (*e.g.*, ranging from 0.01 to 40 mg per kilogram of body weight per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage unit will vary depending, for example, upon the patient being treated and the particular mode of administration. Dosage units will generally contain between from

about 10 µg to about 500 mg of an active ingredient. Optimal dosages may be established using routine testing, and procedures that are well known in the art.

Pharmaceutical compositions may be packaged for treating conditions responsive to VR1 modulation (e.g., treatment of exposure to vanilloid ligand, pain, itch, obesity or urinary incontinence). Packaged pharmaceutical compositions may include a container holding a therapeutically effective amount of at least one VR1 modulator as described herein and instructions (e.g., labeling) indicating that the contained composition is to be used for treating a condition responsive to VR1 modulation in the patient.

METHODS OF USE

VR1 modulators provided herein may be used to alter activity and/or activation of capsaicin receptors in a variety of contexts, both *in vitro* and *in vivo*. Within certain aspects, VR1 antagonists may be used to inhibit the binding of vanilloid ligand agonist (such as capsaicin and/or RTX) to capsaicin receptor *in vitro* or *in vivo*. In general, such methods comprise the step of contacting a capsaicin receptor with a capsaicin receptor modulatory amount of one or more substituted biphenyl-4-carboxylic acid arylamide analogues, or pharmaceutically acceptable forms thereof, in the presence of vanilloid ligand in aqueous solution and under conditions otherwise suitable for binding of the ligand to capsaicin receptor. The capsaicin receptor may be present in solution or suspension (e.g., in an isolated membrane or cell preparation), or in a cultured or isolated cell. Within certain embodiments, the capsaicin receptor is expressed by a neuronal cell present in a patient, and the aqueous solution is a body fluid. Preferably, one or more VR1 modulators are administered to an animal in an amount such that the analogue is present in at least one body fluid of the animal at a therapeutically effective concentration that is 1 micromolar or less; preferably 500 nanomolar or less; more preferably 100 nanomolar or less, 50 nanomolar or less, 20 nanomolar or less, or 10 nanomolar or less. For example, such compounds may be administered at a dose that is less than 20 mg/kg body weight, preferably less than 5 mg/kg and, in some instances, less than 1 mg/kg.

Also provided herein are methods for modulating, preferably inhibiting, the signal-transducing activity of a capsaicin receptor. Such modulation may be achieved by contacting a capsaicin receptor (either *in vitro* or *in vivo*) with a capsaicin receptor modulatory amount of one or more VR1 modulators provided herein under conditions suitable for binding of the modulator(s) to the receptor. The receptor may be present in solution or suspension, in a cultured or isolated cell preparation or within a patient. Modulation of signal transducing

activity may be assessed by detecting an effect on calcium ion conductance (also referred to as calcium mobilization or flux). Modulation of signal transducing activity may alternatively be assessed by detecting an alteration of a symptom (*e.g.*, pain, burning sensation, bronchoconstriction, inflammation, cough, hiccup, itch, and urinary incontinence) of a patient being
5 treated with one or more VR1 modulators provided herein.

VR1 modulator(s) provided herein are preferably administered to a patient (*e.g.*, a human) orally or topically, and are present within at least one body fluid of the animal while modulating VR1 signal-transducing activity. Preferred VR1 modulators for use in such methods modulate VR1 signal-transducing activity *in vitro* at a concentration of 1 nanomolar
10 or less, preferably 100 picomolar or less, more preferably 20 picomolar or less, and *in vivo* at a concentration of 1 micromolar or less, 500 nanomolar or less, or 100 nanomolar or less in a body fluid such as blood.

The present invention further provides methods for treating conditions responsive to VR1 modulation. Within the context of the present invention, the term "treatment"
15 encompasses both disease-modifying treatment and symptomatic treatment, either of which may be prophylactic (*i.e.*, before the onset of symptoms, in order to prevent, delay or reduce the severity of symptoms) or therapeutic (*i.e.*, after the onset of symptoms, in order to reduce the severity and/or duration of symptoms). A condition is "responsive to VR1 modulation" if it is characterized by inappropriate activity of a capsaicin receptor, regardless of the amount
20 of vanilloid ligand present locally, and/or if modulation of capsaicin receptor activity results in alleviation of the condition or a symptom thereof. Such conditions include, for example, symptoms resulting from exposure to VR1-activating stimuli, pain, respiratory disorders such as asthma and chronic obstructive pulmonary disease, itch, urinary incontinence, cough, hiccup, and obesity, as described in more detail below. Such conditions may be diagnosed
25 and monitored using criteria that have been established in the art. Patients may include humans, domesticated companion animals and livestock, with dosages as described above.

Treatment regimens may vary depending on the compound used and the particular condition to be treated. However, for treatment of most disorders, a frequency of administration of 4 times daily or less is preferred. In general, a dosage regimen of 2 times
30 daily is more preferred, with once a day dosing particularly preferred. For the treatment of acute pain, a single dose that rapidly reaches effective concentrations is desirable. It will be understood, however, that the specific dose level and treatment regimen for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of

administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy. In general, the use of the minimum dose sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using medical or veterinary criteria suitable for the condition being treated or prevented.

Patients experiencing symptoms resulting from exposure to capsaicin receptor-activating stimuli include individuals with burns caused by heat, light, tear gas or acid and those whose mucous membranes are exposed (*e.g.*, via ingestion, inhalation or eye contact) to capsaicin (*e.g.*, from hot peppers or in pepper spray) or a related irritant such as acid, tear gas or air pollutants. The resulting symptoms (which may be treated using VR1 modulators, especially antagonists, provided herein) may include, for example, pain, broncho-constriction and inflammation.

Pain that may be treated using the VR1 modulators provided herein may be chronic or acute and includes, but is not limited to, peripheral nerve-mediated pain (especially neuropathic pain). Compounds provided herein may be used in the treatment of, for example, postmastectomy pain syndrome, stump pain, phantom limb pain, oral neuropathic pain, toothache (dental pain), denture pain, postherpetic neuralgia, diabetic neuropathy, reflex sympathetic dystrophy, trigeminal neuralgia, osteoarthritis, rheumatoid arthritis, fibromyalgia, Guillain-Barre syndrome, meralgia paresthetica, burning-mouth syndrome and/or bilateral peripheral neuropathy. Additional neuropathic pain conditions include causalgia (reflex sympathetic dystrophy - RSD, secondary to injury of a peripheral nerve), neuritis (including, for example, sciatic neuritis, peripheral neuritis, polyneuritis, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis and Gombault's neuritis), neuronitis, neuralgias (*e.g.*, those mentioned above, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, migranous neuralgia, idiopathic neuralgia, intercostals neuralgia, mammary neuralgia, mandibular joint neuralgia, Morton's neuralgia, nasociliary neuralgia, occipital neuralgia, red neuralgia, Sluder's neuralgia, splenopalatine neuralgia, supraorbital neuralgia and vidian neuralgia), surgery-related pain, musculoskeletal pain, AIDS-related neuropathy, MS-related neuropathy, and spinal cord injury-related pain. Headache, including headaches involving peripheral nerve activity, such as sinus, cluster (*i.e.*, migranous neuralgia) and some tension headaches and migraine, may also be treated as described herein. For example, migraine headaches may be prevented by administration of a compound provided herein as soon as a pre-migrainous aura is experienced by the patient. Further pain conditions that can be treated as described herein

include "burning mouth syndrome," labor pains, Charcot's pains, intestinal gas pains, menstrual pain, acute and chronic back pain (*e.g.*, lower back pain), hemorrhoidal pain, dyspeptic pains, angina, nerve root pain, homotopic pain and heterotopic pain – including cancer associated pain (*e.g.*, in patients with bone cancer), pain (and inflammation) associated with venom exposure (*e.g.*, due to snake bite, spider bite, or insect sting) and trauma associated pain (*e.g.*, post-surgical pain, pain from cuts, bruises and broken bones, and burn pain). Additional pain conditions that may be treated as described herein include pain associated with inflammatory bowel disease, irritable bowel syndrome and/or inflammatory bowel disease.

Within certain aspects, VR1 modulators provided herein may be used for the treatment of mechanical pain. As used herein, the term "mechanical pain" refers to pain other than headache pain that is not neuropathic or a result of exposure to heat, cold or external chemical stimuli. Mechanical pain includes physical trauma (other than thermal or chemical burns or other irritating and/or painful exposures to noxious chemicals) such as post-surgical pain and pain from cuts, bruises and broken bones; toothache, denture pain; nerve root pain; osteoarthritis; rheumatoid arthritis; fibromyalgia; meralgia paresthetica; back pain; cancer-associated pain; angina; carpal tunnel syndrome; and pain resulting from bone fracture, labor, hemorrhoids, intestinal gas, dyspepsia, and menstruation.

Itching conditions that may be treated include psoriatic pruritis, itch due to hemodialysis, allergic pruritus, and itching associated with vulvar vestibulitis, contact dermatitis, insect bites and skin allergies. Urinary incontinence, as used herein, includes overactive bladder conditions, detrusor hyperflexia of spinal origin and bladder hypersensitivity, all of which may be treated as described herein. In certain such treatment methods, VR1 modulator is administered via a catheter or similar device, resulting in direct injection of VR1 modulator into the bladder. Compounds provided herein may also be used as anti-tussive agents (to prevent, relieve or suppress coughing) and for the treatment of hiccup, and to promote weight loss in an obese patient.

Within other aspects, VR1 modulators provided herein may be used within combination therapy for the treatment of conditions involving inflammatory components. Such conditions include, for example, autoimmune disorders and pathologic autoimmune responses known to have an inflammatory component including, but not limited to, arthritis (especially rheumatoid arthritis), psoriasis, Crohn's disease, lupus erythematosus, irritable bowel syndrome, tissue graft rejection, and hyperacute rejection of transplanted organs.

Other such conditions include trauma (e.g., injury to the head or spinal cord), cardio- and cerebo-vascular disease and certain infectious diseases.

Within such combination therapy, a VR1 modulator is administered to a patient along with an anti-inflammatory agent. The VR1 modulator and anti-inflammatory agent may be present in the same pharmaceutical composition, or may be administered separately in either order. Anti-inflammatory agents include, for example, non-steroidal anti-inflammatory drugs (NSAIDs), non-specific and cyclooxygenase-2 (COX-2) specific cyclooxygenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, tumor necrosis factor (TNF) receptor antagonists, anti-TNF alpha antibodies, anti-C5 antibodies, and interleukin-1 (IL-1) receptor antagonists. Examples of NSAIDs include, but are not limited to ibuprofen (e.g., ADVIL™, MOTRIN™), flurbiprofen (ANSAID™), naproxen or naproxen sodium (e.g., NAPROSYN, ANAPROX, ALEVE™), diclofenac (e.g., CATAFLAM™, VOLTAREN™), combinations of diclofenac sodium and misoprostol (e.g., ARTHROTEC™), sulindac (CLINORIL™), oxaprozin (DAYPRO™), diflunisal (DOLOBID™), piroxicam (FELDENET™), indomethacin (INDOCIN™), etodolac (LODINE™), fenoprofen calcium (NALFON™), ketoprofen (e.g., ORUDIS™, ORUVAIL™), sodium nabumetone (RELAFFEN™), sulfasalazine (AZULFIDINE™), tolmetin sodium (TOLECTIN™), and hydroxychloroquine (PLAQUENIL™). A particular class of NSAIDs consists of compounds that inhibit cyclooxygenase (COX) enzymes, such as celecoxib (CELEBREX™) and rofecoxib (VIOXX™). NSAIDs further include salicylates such as acetylsalicylic acid or aspirin, sodium salicylate, choline and magnesium salicylates (TRILISATE™), and salsalate (DISALCID™), as well as corticosteroids such as cortisone (CORTONE™ acetate), dexamethasone (e.g., DECADRON™), methylprednisolone (MEDROL™) prednisolone (PRELONE™), prednisolone sodium phosphate (PEDIAPRED™), and prednisone (e.g., PREDNICEN-M™, DELTASONE™, STERAPRED™).

Suitable dosages for VR1 modulator within such combination therapy are generally as described above. Dosages and methods of administration of anti-inflammatory agents can be found, for example, in the manufacturer's instructions in the *Physician's Desk Reference*. In certain embodiments, the combination administration of a VR1 modulator with an anti-inflammatory agent results in a reduction of the dosage of the anti-inflammatory agent required to produce a therapeutic effect. Thus, preferably, the dosage of anti-inflammatory agent in a combination or combination treatment method of the invention is less than the maximum dose advised by the manufacturer for administration of the anti-inflammatory agent without combination administration of a VR1 antagonist. More preferably this dosage

is less than $\frac{3}{4}$, even more preferably less than $\frac{1}{2}$, and highly preferably, less than $\frac{1}{4}$ of the maximum dose, while most preferably the dose is less than 10% of the maximum dose advised by the manufacturer for administration of the anti-inflammatory agent(s) when administered without combination administration of a VR1 antagonist. It will be apparent that the dosage amount of VR1 antagonist component of the combination needed to achieve the desired effect may similarly be affected by the dosage amount and potency of the anti-inflammatory agent component of the combination.

In certain preferred embodiments, the combination administration of a VR1 modulator with an anti-inflammatory agent is accomplished by packaging one or more VR1 modulators and one or more anti-inflammatory agents in the same package, either in separate containers within the package or in the same contained as a mixture of one or more VR1 antagonists and one or more anti-inflammatory agents. Preferred mixtures are formulated for oral administration (*e.g.*, as pills, capsules, tablets or the like). In certain embodiments, the package comprises a label bearing indicia indicating that the one or more VR1 modulators and one or more anti-inflammatory agents are to be taken together for the treatment of an inflammatory pain condition. A highly preferred combination is one in which the anti-inflammatory agent(s) include at least one COX-2 specific cyclooxygenase enzyme inhibitor such as valdecoxib (BEXTRA®), lumiracoxib (PREXIGE™), etoricoxib (ARCOXIA®), celecoxib (CELEBREX®) and/or rofecoxib (VIOXX®).

Within further aspects, VR1 modulators provided herein may be used in combination with one or more additional pain relief medications. Certain such medications are also anti-inflammatory agents, and are listed above. Other such medications are narcotic analgesic agents, which typically act at one or more opioid receptor subtypes (*e.g.*, μ , κ and/or δ), preferably as agonists or partial agonists. Such agents include opiates, opiate derivatives and opioids, as well as pharmaceutically acceptable salts and hydrates thereof. Specific examples of narcotic analgesics include, within preferred embodiments, alfentanil, alphaprodine, anileridine, bezitramide, buprenorphine, codeine, diacetyldihydromorphine, diacetylmorphine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levorphan, levorphanol, meperidine, metazocine, methadone, methorphan, metopon, morphine, opium extracts, opium fluid extracts, powdered opium, granulated opium, raw opium, tincture of opium, oxycodone, oxymorphone, paregoric, pentazocine, pethidine, phenazocine, piminodine, propoxyphene, racemethorphan, racemorphan, thebaine and pharmaceutically acceptable salts and hydrates of the foregoing agents.

Other examples of narcotic analgesic agents include acetorphine, acetyldihydrocodeine, acetylmethadol, allylprodine, alphracetylmethadol, alphameprodine, alphamethadol, benzethidine, benzylmorphine, betacetylmethadol, betameprodine, betamethadol, betaprodine, butorphanol, clonitazene, codeine methylbromide, codeine-N-oxide, cyprenorphine, desomorphine, dextromoramide, diampromide, diethylthiambutene, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiamubutene, dioxaphetyl butyrate, dipipanone, drotebanol, ethanol, ethylmethylthiambutene, etonitazene, etorphine, etoxeridine, furethidine, hydromorphenol, hydroxypethidine, ketobemidone, levomoramide, levophenacymorphan, methyl-desorphine, methyldihydromorphine, morpheridine, morphine methylpromide, morphine methylsulfonate, morphine-N-oxide, myrophin, naloxone, nalbuphine, naltrexone, nicocodeine, nicomorphine, noracetylmethadol, norlevorphanol, normethadone, normorphine, norpipanone, pentazocaine, phenadoxone, phenampromide, phenomorphan, phenoperidine, piritramide, pholcodine, proheptazine, properidine, propiran, racemoramide, thebacon, trimeperidine and the pharmaceutically acceptable salts and hydrates thereof.

Further specific representative analgesic agents include, for example: TALWIN® Nx and DEMEROL® (both available from Sanofi Winthrop Pharmaceuticals; New York, NY); LEVO-DROMORAN®; BUPRENEX® (Reckitt & Coleman Pharmaceuticals, Inc.; Richmond, VA); MSIR® (Purdue Pharma L.P.; Norwalk, CT); DILAUDID® (Knoll Pharmaceutical Co.; Mount Olive, NJ); SUBLIMAZE®; SUFENTA® (Janssen Pharmaceutica Inc.; Titusville, NJ); PERCOCET®, NUBAIN® and NUMORPHAN® (all available from Endo Pharmaceuticals Inc.; Chadds Ford, PA); HYDROSTAT® IR, MS/S and MS/L (all available from Richwood Pharmaceutical Co. Inc; Florence, KY), ORAMORPH® SR and ROXICODONE® (both available from Roxanne Laboratories; Columbus OH) and STADOL® (Bristol-Myers Squibb; New York, NY).

Suitable dosages for VR1 modulator within such combination therapy are generally as described above. Dosages and methods of administration of other pain relief medications can be found, for example, in the manufacturer's instructions in the *Physician's Desk Reference*. In certain embodiments, the combination administration of a VR1 modulator with one or more additional pain medications results in a reduction of the dosage of each therapeutic agent required to produce a therapeutic effect (e.g., the dosage of one or both agent may be less than $\frac{3}{4}$, less than $\frac{1}{2}$, less than $\frac{1}{4}$ or less than 10% of the maximum dose listed above or advised by the manufacturer). In certain preferred embodiments, the combination administration of a VR1 modulator with one or more additional pain relief medications is

accomplished by packaging one or more VR1 modulators and one or more additional pain relief medications in the same package, as described above.

Modulators that are VR1 agonists may further be used, for example, in crowd control (as a substitute for tear gas) or personal protection (*e.g.*, in a spray formulation) or as
5 pharmaceutical agents for the treatment of pain, itch or urinary incontinence via capsaicin receptor desensitization. In general, compounds for use in crowd control or personal protection are formulated and used according to conventional tear gas or pepper spray technology.

Within separate aspects, the present invention provides a variety of non-
10 pharmaceutical *in vitro* and *in vivo* uses for the compounds provided herein. For example, such compounds may be labeled and used as probes for the detection and localization of capsaicin receptor (in samples such as cell preparations or tissue sections, preparations or fractions thereof). Compounds may also be used as positive controls in assays for receptor activity, as standards for determining the ability of a candidate agent to bind to capsaicin
15 receptor, or as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT). Such methods can be used to characterize capsaicin receptors in living subjects. For example, a VR1 modulator may be labeled using any of a variety of well known techniques (*e.g.*, radiolabeled with a radionuclide such as tritium, as described herein), and incubated with a sample for a suitable
20 incubation time (*e.g.*, determined by first assaying a time course of binding). Following incubation, unbound compound is removed (*e.g.*, by washing), and bound compound detected using any method suitable for the label employed (*e.g.*, autoradiography or scintillation counting for radiolabeled compounds; spectroscopic methods may be used to detect luminescent groups and fluorescent groups). As a control, a matched sample containing
25 labeled compound and a greater (*e.g.*, 10-fold greater) amount of unlabeled compound may be processed in the same manner. A greater amount of detectable label remaining in the test sample than in the control indicates the presence of capsaicin receptor in the sample. Detection assays, including receptor autoradiography (receptor mapping) of capsaicin receptor in cultured cells or tissue samples may be performed as described by Kuhar in
30 sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York.

Modulators provided herein may also be used within a variety of well known cell separation methods. For example, modulators may be linked to the interior surface of a tissue culture plate or other support, for use as affinity ligands for immobilizing and thereby

isolating, capsaicin receptors (*e.g.*, isolating receptor-expressing cells) *in vitro*. Within one preferred embodiment, a modulator linked to a fluorescent marker, such as fluorescein, is contacted with the cells, which are then analyzed (or isolated) by fluorescence activated cell sorting (FACS).

- 5 The following Examples are offered by way of illustration and not by way of limitation. Unless otherwise specified all reagents and solvent are of standard commercial grade and are used without further purification. Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein.

10 EXAMPLES

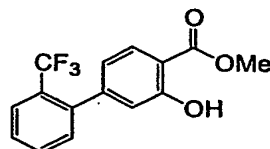
 The following abbreviations appear herein:

	BOP	benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate
	DCM	dichloromethane
15	DME	ethylene glycol dimethyl ether
	DMF	dimethylformamide
	DPPF	1,1'-bis(diphenylphosphino)ferrocene
	EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
	EtOAc	ethyl acetate
20	LiHMDS	lithium bis(trimethylsilyl)amide
	Pd ₂ (dba) ₃	tris[dibenzylideneacetone]di-palladium
	Pd(PPh ₃) ₄	tetrakis(triphenylphosphine) palladium (0)
	THF	tetrahydrofuran
	TLC	thin layer chromatography

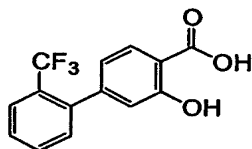
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EXAMPLE 1

PREPARATION OF REPRESENTATIVE BIPHENYL-4-CARBOXYLIC ACID ARYLAMIDE ANALOGUES

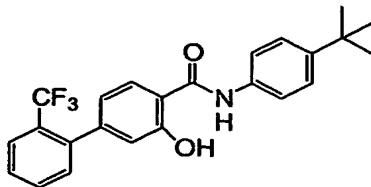
Compound 1. 3-Hydroxy-2'-trifluoromethyl-biphenyl-4-carboxylic acid (4-tert-butyl-phenyl)-amide5 1. *3-Hydroxy-2'-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester*

To a solution of 2-(trifluoromethyl)-phenylboronic acid (5.4 g, 0.03 mol), 2-(dicyclohexylphosphino)biphenyl (133 mg, 0.38 mmol), and potassium phosphate (8.1 g, 0.038 mmol) in toluene, add palladium (II) acetate (43 mg, 0.190 mmol). Purge the reaction mixture for 10 minutes with dry nitrogen and then add 4-chloro-2-hydroxybenzoic acid methyl ester. Heat the stirring reaction mixture overnight at 80°C, cool the mixture and filter through celite using ethyl acetate. Concentrate under reduced pressure, take up in fresh ethyl acetate and wash the solution with NaHCO₃ (saturated aqueous). Dry the solution (Na₂SO₄), concentrate under reduced pressure and then filter through a pad of silica gel using ethyl acetate as eluent. Removal of solvent under reduced pressure gives 3-hydroxy-2'-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester as an oil.

2. *3-hydroxy-2'-trifluoromethyl-biphenyl-4-carboxylic acid*

Dissolve 3-hydroxy-2'-trifluoromethyl-biphenyl-4-carboxylic acid methyl ester (200 mg, 0.675 mmol) in methyl alcohol (15 mL) and add 10N NaOH solution (1mL). Stir the reaction mixture overnight at room temperature. Remove the solvent under reduced pressure and dissolve the residue in water. Acidify the solution with 2N HCl and collect the precipitate. Wash the solid with water and dry to afford 3-hydroxy-2'-trifluoromethyl-biphenyl-4-carboxylic acid.

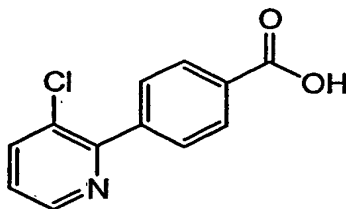
3. *3-Hydroxy-2'-trifluoromethyl-biphenyl-4-carboxylic acid (4-tert-butyl-phenyl)-amide*



- Stir a mixture of 3-hydroxy-2'-trifluoromethyl-biphenyl-4-carboxylic acid (100 mg, 0.354 mmol), 4-*t*-butyl-aniline (53 mg, 0.354 mmol), BOP (156 mg, 0.354 mmol) and triethylamine (36 mg, 0.354 mmol) in DMF (3mL) at 80°C for 6 hours. Partition the mixture between ethyl acetate and water. Wash the organic layer with 3M HCl solution (2X) followed by brine (1X). Dry the organic layer (Na₂SO₄) and concentrate under reduced pressure. Triturate the residue with hexanes to give 3-hydroxy-2'-trifluoromethyl-biphenyl-4-carboxylic acid (4-*tert*-butyl-phenyl)-amide as a solid.

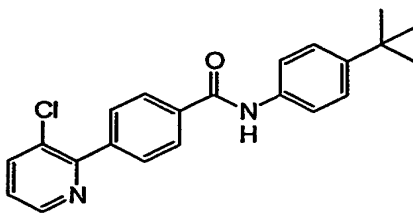
10 Compound 2. *N*-(4-*tert*-Butyl-phenyl)-4-(3-chloro-pyridin-2-yl)-benzamide

1. *4-(3-Chloro-pyridin-2-yl)-benzoic acid*



- Bubble nitrogen through a solution of 4-carboxyphenylboronic acid (1.82 g, 0.11 mol), 2,3-dichloropyridine (1.08 g, 0.0073 mol), 2M Na₂CO₃ (9.1 mL, 2.5 equivalents), in acetonitrile for 10 minutes. Add Pd(PPh₃)₄ (422 mg) and bubble nitrogen through the solution for two additional minutes. Heat the reaction for 24 hours at 80°C. Cool the reaction, and partition between 10% NaOH and ether. Wash the aqueous layer with ether (2X) and then acidify with acetic acid to give a white solid. The solid was collected and recrystallized from boiling MeOH/water to give 4-(3-chloro-pyridin-2-yl)-benzoic acid.

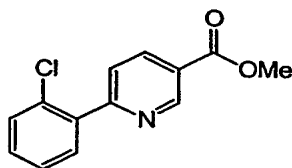
20 2. *N*-(4-*tert*-Butyl-phenyl)-4-(3-chloro-pyridin-2-yl)-benzamide



Heat a solution of 4-(3-chloro-pyridin-2-yl)-benzoic acid (83 mg, 0.355 mmol), 4-*t*-butyl-aniline (106 mg, 0.71 mmol), BOP reagent (157 mg, 0.355 mmol) and triethylamine (0.355 mmol) in DMF at 80°C for 12 hours. Cool, dilute with water, and extract with ethyl acetate. Wash the ethyl acetate sequentially with 10% NaOH, 50% aqueous acetic acid, 10% NaOH, and brine. Dry the solution (Na₂SO₄) and concentrate under reduced pressure to give the crude product as an oil. Purify using preparative TLC plates (2 x 2000 micron; 20% ethyl acetate/hexanes eluent) to give *N*-(4-*tert*-butyl-phenyl)-4-(3-chloro-pyridin-2-yl)-benzamide as a solid.

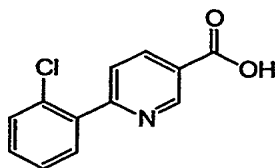
Compound 3. *N*-(4-*tert*-Butyl-phenyl)-6-(2-chloro-phenyl)-nicotinamide

1. 6-(2-Chloro-phenyl)-nicotinic acid methyl ester



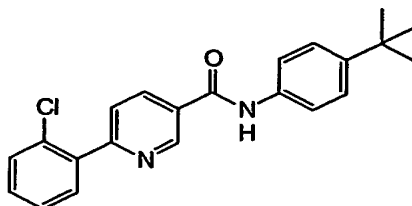
Purge a solution of 2-chloro-phenylboronic acid (5.17g, 0.033 mol), 6-chloro-nicotinic acid methyl ester (2.83g, 0.0165 mol), 2M Na₂CO₃ (20 mL, 0.04 mol), and dimethoxyethane with nitrogen gas for 10 minutes. Add Pd(PPh₃)₄ (1.15 g) and heat the mixture at reflux for 12 hours. Cool the solution and concentrate it under reduced pressure. Dilute with water and extract the aqueous with ethyl acetate. Dry the ethyl acetate (Na₂SO₄) and concentrate under reduced pressure to give the crude product. Purify via flash column chromatography (5% ethyl acetate/ hexanes to 15% ethyl acetate/hexanes) to give 6-(2-chloro-phenyl)-nicotinic acid methyl ester.

2. 6-(2-Chloro-phenyl)-nicotinic acid



Dissolve 6-(2-chloro-phenyl)-nicotinic acid methyl ester (1.57 g, 0.0063 mol) in THF and add about a tenth volume of methanol. Add water followed by LiOH.H₂O (794 mg, 0.019 mol) and reflux for 12 hours. Remove the solvents, add water, wash the aqueous with ether (2x). Bring the aqueous solution to pH ~6 with 3N HCl solution. Collect the white precipitate and wash with water to give 6-(2-chloro-phenyl)-nicotinic acid.

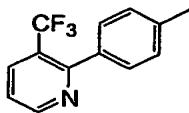
3. *N*-(4-*tert*-Butyl-phenyl)-6-(2-chloro-phenyl)-nicotinamide



Heat a solution of 6-(2-chloro-phenyl)-nicotinic acid (83 mg, 0.355 mmol), 4-*t*-butylaniline (106 mg, 0.71 mmol), BOP reagent (157 mg, 0.355 mmol), and triethylamine (36 mg, 0.355 mmol) in DMF at 80°C for 12 hours. Cool the solution, dilute it with water and extract with ethyl acetate. Wash the ethyl acetate portion with 10% NaOH (1x), 50% aqueous HOAc (2x), 10% NaOH (1x) and then dry (Na₂SO₄) and concentrate under reduced pressure. Purify the crude material using preparative thin layer chromatography (2 x 2mm silica gel plates eluting with 20% ethyl acetate/hexanes) to obtain *N*-(4-*tert*-butyl-phenyl)-6-(2-chloro-phenyl)-nicotinamide.

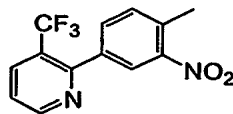
Compound 4. *N*-(4-*tert*-Butyl-phenyl)-2-hydroxy-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide

1. *2-p*-tolyl-3-trifluoromethyl-pyridine

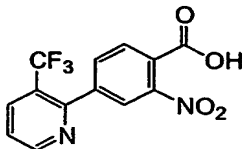


To a de-gassed mixture of 2-chloro-3-(trifluoromethyl)-pyridine (70.1 mmol), *p*-tolylboronic acid (70.6 mmol), and 2M Na₂CO₃ (175.0 mmol), in DME (200 mL) under nitrogen add Pd(PPh₃)₄ (2.8 mmol). Stir the mixture at 80°C for overnight, concentrate, and extract with EtOAc. Dry over Na₂SO₄, concentrate under vacuum, and pass through silica gel pad to give 2-*p*-tolyl-3-trifluoromethyl-pyridine.

2. 2-(4-methyl-3-nitro-phenyl)-3-(trifluoromethyl)-pyridine

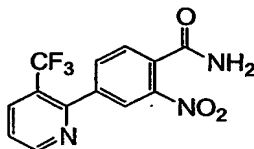


To a solution of 2-*p*-tolyl-3-trifluoromethyl-pyridine (8.4 mmol) in H₂SO₄ (6 mL) cautiously add fuming HNO₃ (2 mL). Stir the mixture 60 minutes at room temperature. Pour the mixture onto ice-water (30 mL), extract with EtOAc, neutralize with 1 N NaOH, dry over Na₂SO₄, and concentrate under vacuum to obtain 2-(4-methyl-3-nitro-phenyl)-3-(trifluoromethyl)-pyridine.

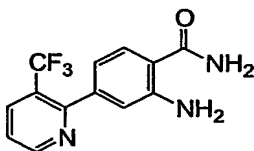
3. *2-nitro-4-(3-trifluoromethyl-pyridin-2-yl)-benzoic acid*

To a solution of 2-(4-methyl-3-nitro-phenyl)-3-(trifluoromethyl)-pyridine (7.1 mmol) in the mixture of pyridine (10 mL) and water (5 mL) add KMnO_4 (25.3 mmol) portionwise.

- 5 Stir the mixture for 4 hours at 110°C then add another 25.3 mmol of KMnO_4 with 10 mL of water. Stir the mixture at 110°C for overnight. Cool to room temperature, filter through celite pad. Concentrate the filtrate under vacuum, dilute with water, and wash the aqueous with EtOAc. Neutralize the aqueous with 2 N HCl and collect the precipitate to give 2-nitro-4-(3-trifluoromethyl-pyridin-2-yl)-benzoic acid.

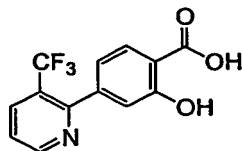
10 4. *2-nitro-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide*

- Reflux the mixture of 2-nitro-4-(3-trifluoromethyl-pyridin-2-yl)-benzoic acid (25 g) with SOCl_2 (50 mL) for 4 hours and concentrate. Dissolve the residue in dichloromethane, cool with ice-water bath, pass NH_3 gas through the solution for 30 minutes, and stir for 15 minutes at room temperature. Concentrate and wash with water to give 2-nitro-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide.

5. *2-amino-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide*

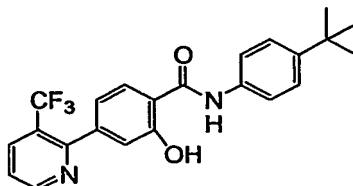
- Hydrogenate the solution of 2-nitro-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide (3.84 mmol) in 95% EtOH (100 mL) with 10% Pd-C (150 mg) for overnight. Filter through a celite pad and concentrate the filtrate to give 2-amino-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide.

6. *2-Hydroxy-4-(3-trifluoromethyl-pyridin-2-yl)-benzoic acid*



To a cooled solution (0°C) of 2-amino-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide (1.0 g, 3.56 mmol) in 70% H₂SO₄ (25 ml), add NaNO₂ (282 mg, 4.09 mmol) solution in H₂O (5 ml). Stir the mixture for 15 minutes at 0°C. Heat the stirring reaction mixture 4 hours at 130°C, cool the mixture and neutralize to pH 3-4 with 10N NaOH. Extract with EtOAc, wash with brine, and concentrate under reduced pressure to give pure 2-hydroxy-4-(3-trifluoromethyl-pyridin-2-yl)-benzoic acid as a solid.

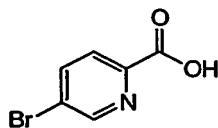
7. *N-(4-tert-Butyl-phenyl)-2-hydroxy-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide*



Stir a mixture of pure 2-hydroxy-4-(3-trifluoromethyl-pyridin-2-yl)-benzoic acid (100 mg, 0.354 mmol), 4-*t*-butyl-aniline (53 mg, 0.354 mmol), BOP reagent (156 mg, 0.354 mmol) and triethylamine (36 mg, 0.354 mmol) in DMF (3mL) at 80°C for 6 hours. Partition the mixture between ethyl acetate and water. Wash the organic layer with brine (1x). Dry the organic layer (Na₂SO₄) and concentrate under reduced pressure. Purify using preparative TLC plates (2 X 2000 micron/ 5% MeOH/EtOAc eluent) to give *N*-(4-*tert*-butyl-phenyl)-2-hydroxy-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide as a solid.

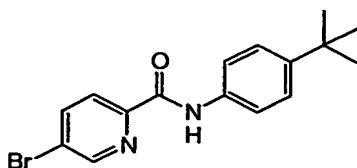
Compound 5. 5-(2-Chloro-phenyl)-pyridine-2-carboxylic acid (4-*tert*-butyl-phenyl)-amide

1. *5-Bromo-pyridine-2-carboxylic acid hydrochloride*



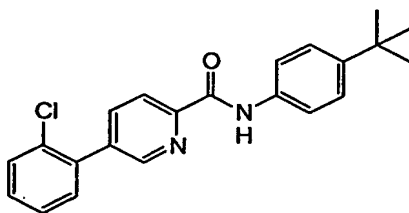
Reflux a mixture of 5-bromo-pyridine-2-carbonitrile (560 mg) in conc. HCl (15 ml) for 12 hours. Cool to room temperature, collect the precipitate, and wash with ether to give 5-bromo-pyridine-2-carboxylic acid hydrochloride as a solid.

2. *5-Bromo-pyridine-2-carboxylic acid (4-tert-butyl-phenyl)-amide*



Heat a solution of 5-bromo-pyridine-2-carboxylic acid hydrochloride (238 mg, 1.0 mmol), 4-*t*-butyl-aniline (149 mg, 1.0 mmol), BOP reagent (424 mg, 1.0 mmol) and triethylamine (2.0 mmol) in DMF at 80°C for 12 hours. Cool, dilute with water, and extract with ethyl acetate. Wash the ethyl acetate sequentially with 10% NaOH, 50% aqueous acetic acid, and brine. Dry the solution (Na₂SO₄) and concentrate under reduced pressure to give the crude product. Purify using preparative TLC plates (2 x 2000 micron; 25% ethyl acetate/hexanes eluent) to give 5-bromo-pyridine-2-carboxylic acid (4-*tert*-butyl-phenyl)-amide as a solid.

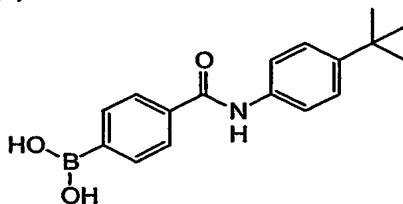
3. 5-(2-Chloro-phenyl)-pyridine-2-carboxylic acid (4-*tert*-butyl-phenyl)-amide



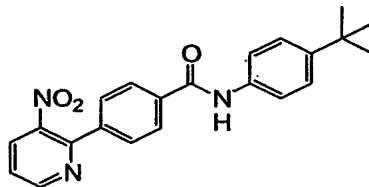
Bubble nitrogen through a solution of 2-chlorophenylboronic acid (108 mg, 0.69 mmol), 5-bromo-pyridine-2-carboxylic acid (4-*tert*-butyl-phenyl)-amide (115 mg, 0.35 mmol), 2M Na₂CO₃ (0.43 ml, 2.5 equivalents), in DME for 10 minutes. Add Pd(PPh₃)₄ (16 mg) and bubble nitrogen through the solution for two additional minutes. Heat the reaction for 12 hours at 80°C. Cool the reaction, concentrate, and partition between EtOAc and water. Dry the solution (Na₂SO₄) and concentrate under reduced pressure to give the crude product. Purify using preparative TLC plates (2 x 2000 micron; 25% ethyl acetate/hexanes eluent) to give 5-(2-chloro-phenyl)-pyridine-2-carboxylic acid (4-*tert*-butyl-phenyl)-amide as a solid.

EXAMPLE 2

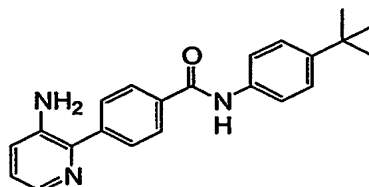
PREPARATION OF ADDITIONAL BIPHENYL-4-CARBOXYLIC ACID ARYLAMIDE ANALOGUES

Compound 6. *N*-(4-*tert*-Butyl-phenyl)-4-(3-methanesulfonylamino-pyridin-2-yl)-benzamide1. 4-Borono-*N*-(4-*tert*-Butyl-phenyl)-benzamide

Heat a solution of 4-carboxyphenylboronic acid (5.0 g, 30.1 mmol), 4-*t*-butyl-aniline (4.5 g, 30.1 mmol), BOP reagent (13.3 g, 30.1 mmol) and triethylamine (30.1 mmol) in DMF at 80°C for 12 hours. Cool, dilute with water, and collect the precipitate. Wash with water and hexanes to give 4-borono-*N*-(4-*tert*-butyl-phenyl)-benzamide as a solid.

2. *N*-(4-*tert*-Butyl-phenyl)-4-(3-nitro-pyridin-2-yl)-benzamide

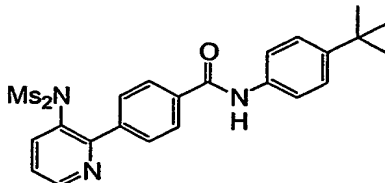
Bubble nitrogen through a solution of 4-borono-*N*-(4-*tert*-butyl-phenyl)-benzamide (1.3 g, 4.37 mmol), 2-bromo-3-nitro-pyridine (0.63 g, 3.12 mmol), 2M Na₂CO₃ (3.9 ml, 2.5 equivalents), in DME for 10 minutes. Add Pd(PPh₃)₄ (144 mg) and bubble nitrogen through the solution for two additional minutes. Heat the reaction for 12 hours at 80°C. Cool the reaction, concentrate, and partition between EtOAc and water. Dry the solution (Na₂SO₄) and concentrate under reduced pressure to give the crude product. Purify using chromatography (25% ethyl acetate/hexanes eluent) to give *N*-(4-*tert*-butyl-phenyl)-4-(3-nitro-pyridin-2-yl)-benzamide as a solid.

3. 4-(3-Amino-pyridin-2-yl)-*N*-(4-*tert*-butyl-phenyl)-benzamide

Hydrogenate the solution of *N*-(4-*tert*-butyl-phenyl)-4-(3-nitro-pyridin-2-yl)-benzamide (2.2 mmol) in EtOH-EtOAc (1:1, 100 mL) with 10%Pd-C (600 mg) for overnight.

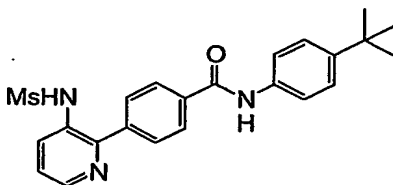
Filter through a celite pad, concentrate the filtrate, and triturate with ether to give 4-(3-amino-pyridin-2-yl)-N-(4-*tert*-butyl-phenyl)-benzamide as a solid.

4. *N*-(4-*tert*-Butyl-phenyl)-4-(3-bis-methanesulfonylamino-pyridin-2-yl)-benzamide



- 5 To a solution of 4-(3-amino-pyridin-2-yl)-N-(4-*tert*-butyl-phenyl)-benzamide (400 mg, 1.16 mmol) and triethylamine (230 mg, 2.32 mmol) in DCM (100 ml) add methanesulfonyl chloride (266 mg, 2.32 mmol) dropwise. Stir the mixture 10 minutes at room temperature. Concentrate and partition between EtOAc and water. Dry the solution (Na₂SO₄), concentrate under reduced pressure, and triturate with ether-hexanes to give N-(4-*tert*-butyl-phenyl)-4-(3-bismethanesulfonylamino-pyridin-2-yl)-benzamide as a solid.

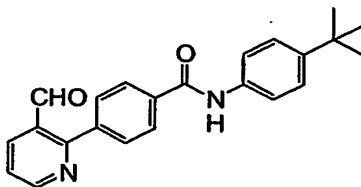
5. *N*-(4-*tert*-Butyl-phenyl)-4-(3-methanesulfonylamino-pyridin-2-yl)-benzamide



- 15 Stir the mixture of N-(4-*tert*-butyl-phenyl)-4-(3-bismethanesulfonylamino-pyridin-2-yl)-benzamide (0.6 mmol) and diethylamine (5 equivalents) in DCM-MeOH (1:1, 20 ml) overnight at room temperature. Concentrate and purify using chromatography (5% MeOH/EtOAc eluent) to give N-(4-*tert*-butyl-phenyl)-4-(3-methanesulfonylamino-pyridin-2-yl)-benzamide as a solid.

Compound 7. *N*-(4-*tert*-Butyl-phenyl)-4-(3-pyrrolidin-1-ylmethyl-pyridin-2-yl)-benzamide

1. *N*-(4-*tert*-Butyl-phenyl)-4-(3-formyl-pyridin-2-yl)-benzamide

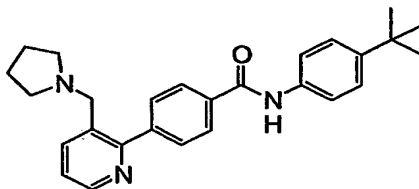


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Bubble nitrogen through a solution of 4-borono-N-(4-*tert*-butyl-phenyl)-benzamide (2.9 g, 9.76 mmol), 2-chloro-3-formyl-pyridine (0.92 g, 6.50 mmol), 2M Na₂CO₃ (6.5 ml, 2.0 equivalents), in DME for 10 minutes. Add Pd(PPh₃)₄ (300 mg) and bubble nitrogen through

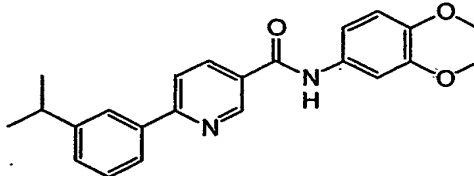
the solution for two additional minutes. Heat the reaction for 12 hours at 80°C. Cool the reaction, concentrate, and partition between EtOAc and water. Dry the solution (Na₂SO₄) and concentrate under reduced pressure to give the crude product. Purify using chromatography (50% ethyl acetate/hexanes eluent) to give N-(4-*tert*-butyl-phenyl)-4-(3-formyl-pyridin-2-yl)-benzamide as a solid.

2. *N*-(4-*tert*-Butyl-phenyl)-4-(3-pyrrolidin-1-ylmethyl-pyridin-2-yl)-benzamide



Stir the mixture of N-(4-*tert*-butyl-phenyl)-4-(3-formyl-pyridin-2-yl)-benzamide (150 mg, 0.42 mmol), pyrrolidine (30 mg, 0.42 mmol), HOAc (0.025ml, 0.42 mmol), and NaBHAc₃ (124 mg, 0.58 mmol) in dichloroethane (5 ml) overnight at room temperature. Concentrate and purify using preparative TLC plates (2 x 2000 micron; 10:90:1 MeOH/DCM/NH₄OH eluent) to give N-(4-*tert*-butyl-phenyl)-4-(3-pyrrolidin-1-ylmethyl-pyridin-2-yl)-benzamide.

Compound 8. N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(3-isopropyl-phenyl)-nicotinamide



Prepare this compound in a manner analogous to that used for compound 3 using 3-isopropyl-phenylboronic acid, 6-chloro-nicotinic acid methyl ester, and 2,3-dihydro-benzo[1,4]dioxin-6-ylamine. Observed Mass Spec (M+H) = 375.

EXAMPLE 3

ADDITIONAL REPRESENTATIVE BIPHENYL-4-CARBOXYLIC ACID ARYLAMIDE ANALOGUES

Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce other compounds encompassed by the present invention. Compounds listed in Table I were prepared using the above methods, with readily apparent modifications. In the column labeled K_i, * indicates that the K_i determined as described in Example 5, herein, is 1 micromolar or less.

Mass spectroscopy data shown in Table I is Electrospray MS, obtained in positive ion mode with a 15V or 30V cone voltage, using a Micromass Time-of-Flight LCT, equipped with a Waters 600 pump, Waters 996 photodiode array detector, Gilson 215 autosampler, and a Gilson 841 microinjector. MassLynx (Advanced Chemistry Development, Inc; Toronto, Canada) version 4.0 software was used for data collection and analysis. Sample volume of 1 microliter was injected onto a 50x4.6mm Chromolith SpeedROD C18 column, and eluted using a 2-phase linear gradient at 6ml/min flow rate. Sample was detected using total absorbance count over the 220-340nm UV range. The elution conditions were: Mobile Phase A- 95/5/0.05 Water/Methanol/TFA; Mobile Phase B-5/95/0.025 Water/Methanol/TFA.

10

Gradient:	Time(min)	%B
	0	10
	0.5	100
	1.2	100
	1.21	10

15

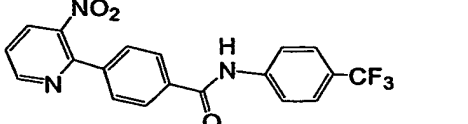
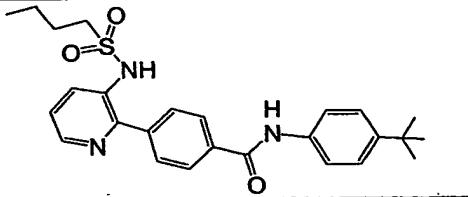
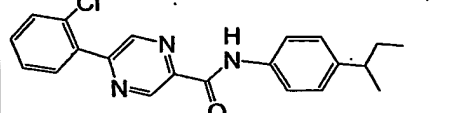
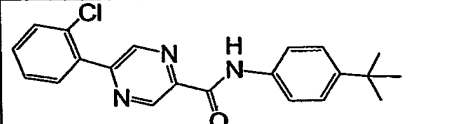
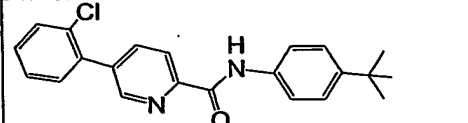
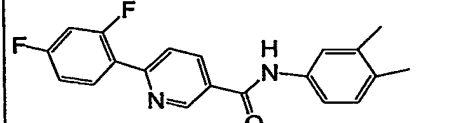
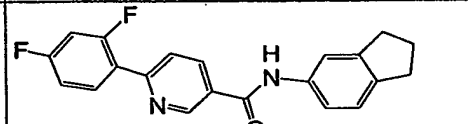
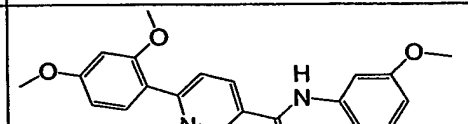
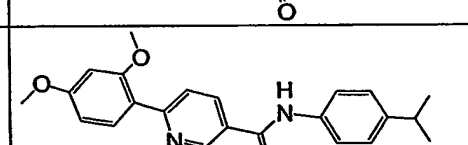
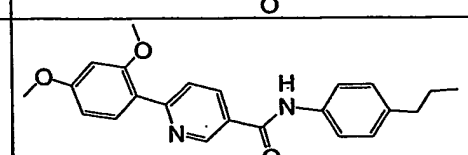
The total run time was 2 minutes inject to inject. Data is presented as mass + 1 (M+1).

Table I - Representative Biphenyl-4-Carboxylic Acid Arylamide Analogues

	Compound	Name	(M+1)	K _i
9.		[2,2']Bipyridinyl-5-carboxylic acid (4- <i>tert</i> -butyl-phenyl)-amide	332.18	*
10.		[2,2']Bipyridinyl-5-carboxylic acid (4-trifluoromethyl-phenyl)-amide	344.12	
11.		[2,4']Bipyridinyl-5-carboxylic acid (4- <i>tert</i> -butyl-phenyl)-amide	332.22	*
12.		2-Amino-N-(4- <i>tert</i> -butyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide	414.09	*
13.		2-Amino-N-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide	504.06	*
14.		2-Amino-N-(6-trifluoromethyl-pyridin-3-yl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide	427.02	*

	Compound	Name	(M+1)	K _i
15.		2'-Chloro-biphenyl-4-carboxylic acid (4- <i>tert</i> -butyl-phenyl)-amide	364.18	*
16.		2-Hydroxy-N-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide	427.08	*
17.		2-Methanesulfonylamino-N-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide	504.21	*
18.		2-Nitro-N-(4-trifluoromethanesulfonyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide		*
19.		2-Nitro-N-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide	456.08	*
20.		2-Nitro-N-(6-trifluoromethyl-pyridin-3-yl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide	535.03	*
21.		3-Hydroxy-2'-trifluoromethyl-biphenyl-4-carboxylic acid (4- <i>tert</i> -butyl-phenyl)-amide	414.22	*
22.		4-(1-Acetyl-piperidin-2-yl)-N-(4- <i>tert</i> -butyl-phenyl)-benzamide	379.2	*
23.		4-(3-Amino-pyridin-2-yl)-N-(4- <i>tert</i> -butyl-phenyl)-benzamide	346.21	*
24.		4-(3-Amino-pyridin-4-yl)-N-(4- <i>tert</i> -butyl-phenyl)-benzamide	346.24	*

	Compound	Name	(M+1)	K _i
25.		4-(3-Benzenesulfonylamino-pyridin-2-yl)-N-(4- <i>tert</i> -butyl-phenyl)-benzamide	486.23	*
26.		4-(3-Chloro-pyridin-2-yl)-N-(4-isopropyl-3-methyl-phenyl)-benzamide	365.19	*
27.		4-(3-Chloro-pyridin-2-yl)-N-(4-isopropyl-phenyl)-benzamide	351.14	*
28.		4-(3-Chloro-pyridin-2-yl)-N-(5-trifluoromethyl-pyridin-2-yl)-benzamide	378.08	*
29.		4-(3-Chloro-pyridin-2-yl)-N-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-benzamide	367.14	*
30.		4-(3-Chloro-pyridin-2-yl)-N-[4-(2,2,2-trifluoro-1-methyl-ethyl)-phenyl]-benzamide	405.16	*
31.		4-(3-Chloro-pyridin-2-yl)-N-[4-(2-methoxy-1,1-dimethyl-ethyl)-phenyl]-benzamide	395.19	*
32.		4-(3-Chloro-pyridin-2-yl)-N-[4-(cyano-dimethyl-methyl)-phenyl]-benzamide	376.15	*
33.		4-(3-Fluoro-pyridin-2-yl)-N-(4-isopropyl-3-methyl-phenyl)-benzamide	349.19	*
34.		4-(3-Fluoro-pyridin-2-yl)-N-(4-isopropyl-phenyl)-benzamide	335.18	*
35.		4-(3-Fluoro-pyridin-2-yl)-N-(4-trifluoromethyl-phenyl)-benzamide	361.13	*

	Compound	Name	(M+1)	K _i
36.		4-(3-Nitro-pyridin-2-yl)-N-(4-trifluoromethyl-phenyl)-benzamide		*
37.		4-[3-(Butane-1-sulfonylamino)-pyridin-2-yl]-N-(4-tert-butyl-phenyl)-benzamide	466.28	*
38.		5-(2-Chloro-phenyl)-pyrazine-2-carboxylic acid (4-sec-butyl-phenyl)-amide		*
39.		5-(2-Chloro-phenyl)-pyrazine-2-carboxylic acid (4-tert-butyl-phenyl)-amide		*
40.		5-(2-Chloro-phenyl)-pyridine-2-carboxylic acid (4-tert-butyl-phenyl)-amide	365.17	*
41.		6-(2,4-Difluoro-phenyl)-N-(3,4-dimethyl-phenyl)-nicotinamide	339.11	
42.		6-(2,4-Difluoro-phenyl)-N-indan-5-yl-nicotinamide	351.11	
43.		6-(2,4-Dimethoxy-phenyl)-N-(3-methoxy-phenyl)-nicotinamide	365.16	
44.		6-(2,4-Dimethoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide	377.18	
45.		6-(2,4-Dimethoxy-phenyl)-N-(4-propyl-phenyl)-nicotinamide	377.17	

	Compound	Name	(M+1)	K _i
46.		6-(2,4-Dimethoxy-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide	403.16	
47.		6-(2,5-Dimethoxy-phenyl)-N-(3-methoxy-phenyl)-nicotinamide	365.16	
48.		6-(2,5-Dimethoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide	377.18	
49.		6-(2,5-Dimethoxy-phenyl)-N-(4-propyl-phenyl)-nicotinamide	377.18	
50.		6-(2,5-Dimethyl-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide	335.15	
51.		6-(2,5-Dimethyl-phenyl)-N-(3-methoxy-phenyl)-nicotinamide	333.16	
52.		6-(2,5-Dimethyl-phenyl)-N-(4-ethyl-phenyl)-nicotinamide	331.17	
53.		6-(2,5-Dimethyl-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide	345.18	
54.		6-(2,5-Dimethyl-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide	388.25	
55.		6-(2,5-Dimethyl-phenyl)-N-(4-propyl-phenyl)-nicotinamide	345.19	
56.		6-(2,5-Dimethyl-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide	371.16	*

	Compound	Name	(M+1)	K _i
57.		6-(2,5-Dimethyl-phenyl)-N-indan-5-yl-nicotinamide	343.17	
58.		6-(2,6-Dimethoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide	377.18	
59.		6-(2,6-Dimethoxy-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide	403.15	
60.		6-(2-Acetyl-phenyl)-N-(4-tert-butyl-phenyl)-nicotinamide	373.22	*
61.		6-(2-Amino-phenyl)-N-(4-tert-butyl-phenyl)-nicotinamide	346.21	*
62.		6-(2-Chloro-phenyl)-N-(2,3,4-trifluoro-phenyl)-nicotinamide	363.12	
63.		6-(2-Chloro-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide	380.20	
64.		6-(2-Chloro-phenyl)-N-(2-trifluoromethyl-phenyl)-nicotinamide	377.09	*
65.		6-(2-Chloro-phenyl)-N-(3,4-dichloro-phenyl)-nicotinamide	377.09	
66.		6-(2-Chloro-phenyl)-N-(3,4-difluoro-phenyl)-nicotinamide	345.12	
67.		6-(2-Chloro-phenyl)-N-(3,5-dichloro-phenyl)-nicotinamide	377.09	

	Compound	Name	(M+1)	K _i
68.		6-(2-Chloro-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide	341.13	
69.		6-(2-Chloro-phenyl)-N-(3-fluoro-phenyl)-nicotinamide	327.11	
70.		6-(2-Chloro-phenyl)-N-(3-methoxy-phenyl)-nicotinamide	339.16	
71.		6-(2-Chloro-phenyl)-N-(3-trifluoromethyl-phenyl)-nicotinamide	377.13	
72.		6-(2-Chloro-phenyl)-N-(4-difluoromethoxy-phenyl)-nicotinamide	375.13	
73.		6-(2-Chloro-phenyl)-N-(4-ethyl-phenyl)-nicotinamide	337.18	
74.		6-(2-Chloro-phenyl)-N-(4-fluoro-phenyl)-nicotinamide	327.11	
75.		6-(2-Chloro-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide	351.20	
76.		6-(2-Chloro-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide	279.15	
77.		6-(2-Chloro-phenyl)-N-(4-propyl-phenyl)-nicotinamide	351.20	*
78.		6-(2-Chloro-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide	377.10	*

	Compound	Name	(M+1)	K _i
79.		6-(2-Chloro-phenyl)-N-[4-(4,5-dichloro-imidazol-1-yl)-phenyl]-nicotinamide	443.19	
80.		6-(2-Chloro-phenyl)-N-m-tolyl-nicotinamide	323.16	
81.		6-(2-Chloro-phenyl)-N-phenyl-nicotinamide	309.06	*
82.		6-(2-Chloro-phenyl)-N-quinolin-3-yl-nicotinamide	360.14	*
83.		6-(2-Fluoro-phenyl)-N-(1-oxo-indan-5-yl)-nicotinamide	347.18	
84.		6-(2-Fluoro-phenyl)-N-(2-fluoro-5-trifluoromethyl-phenyl)-nicotinamide	379.15	
85.		6-(2-Fluoro-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide	364.18	*
86.		6-(2-Fluoro-phenyl)-N-(2-methyl-quinolin-6-yl)-nicotinamide	358.23	
87.		6-(2-Fluoro-phenyl)-N-(3-methoxy-phenyl)-nicotinamide	323.17	*
88.		6-(2-Fluoro-phenyl)-N-(3-trifluoromethyl-phenyl)-nicotinamide	361.10	*
89.		6-(2-Fluoro-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide	335.20	*

	Compound	Name	(M+1)	K _i
90.		6-(2-Fluoro-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide	279.13	
91.		6-(2-Fluoro-phenyl)-N-(4-propyl-phenyl)-nicotinamide	335.16	*
92.		6-(2-Fluoro-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide	361.17	*
93.		6-(2-Fluoro-phenyl)-N-indan-5-yl-nicotinamide	333.19	*
94.		6-(2-Fluoro-phenyl)-N-m-tolyl-nicotinamide	307.17	
95.		6-(2-Fluoro-phenyl)-N-phenyl-nicotinamide	293.15	
96.		6-(2-Methoxy-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide	376.23	
97.		6-(2-Methoxy-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide	390.22	
98.		6-(2-Methoxy-phenyl)-N-(4-propyl-phenyl)-nicotinamide	347.17	
99.		6-(2-Methoxy-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide	373.13	*
100.		6-(2-Methylsulfanyl-phenyl)-N-(4-propyl-phenyl)-nicotinamide	363.14	

	Compound	Name	(M+1)	K _i
101.		6-(2-Methylsulfanyl-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide	389.13	
102.		6-(3,4-Difluoro-phenyl)-N-(3,4-dimethyl-phenyl)-nicotinamide	339.11	
103.		6-(3,4-Difluoro-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide	343.09	
104.		6-(3,4-Difluoro-phenyl)-N-indan-5-yl-nicotinamide	351.11	
105.		6-(3,4-Dimethoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide	377.28	
106.		6-(3,4-Dimethyl-phenyl)-N-(4-ethyl-phenyl)-nicotinamide	331.23	
107.		6-(3,4-Dimethyl-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide	345.24	
108.		6-(3,4-Dimethyl-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide	388.32	
109.		6-(3,4-Dimethyl-phenyl)-N-indan-5-yl-nicotinamide	343.23	*
110.		6-(3,5-Dimethyl-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide	335.20	*

	Compound	Name	(M+1)	K _i
111.		6-(3,5-Dimethyl-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide	388.31	
112.		6-(3,5-Dimethyl-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide	371.23	
113.		6-(3-Chloro-phenyl)-N-(3,4-dimethyl-phenyl)-nicotinamide	337.09	
114.		6-(3-Chloro-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide	341.07	
115.		6-(3-Chloro-phenyl)-N-(4-ethyl-phenyl)-nicotinamide	337.10	
116.		6-(3-Chloro-phenyl)-N-indan-5-yl-nicotinamide	349.10	*
117.		6-(3-Cyano-phenyl)-N-(3,4-dimethyl-phenyl)-nicotinamide	328.13	
118.		6-(3-Cyano-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide	342.15	
119.		6-(3-Ethoxy-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide	390.23	*
120.		6-(3-Ethoxy-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide	351.21	*

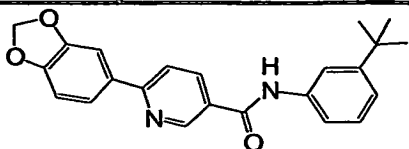
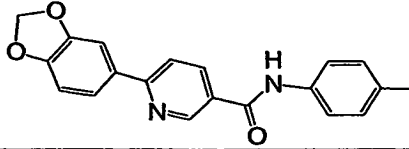
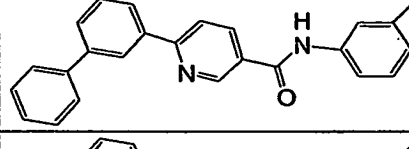
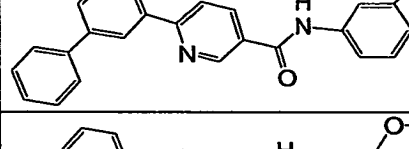
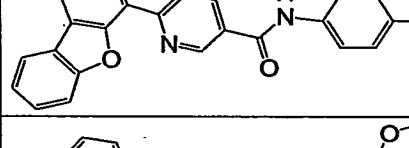
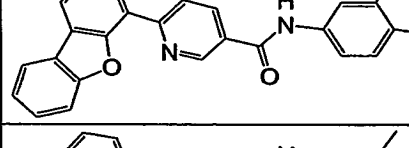
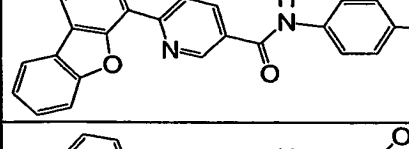
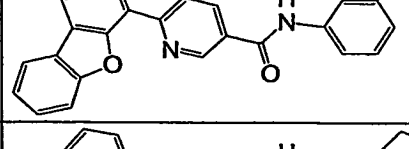
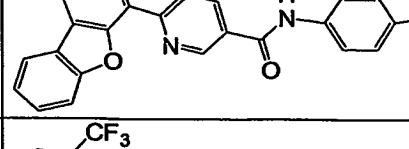
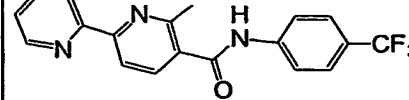
	Compound	Name	(M+1)	K _i
121.		6-(3-Ethoxy-phenyl)-N-(3-methoxy-phenyl)-nicotinamide	349.21	
122.		6-(3-Ethoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide	361.26	
123.		6-(3-Ethoxy-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide	387.22	
124.		6-(3-Ethoxy-phenyl)-N-indan-5-yl-nicotinamide	359.24	*
125.		6-(3-Fluoro-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide	364.19	*
126.		6-(3-Fluoro-phenyl)-N-(3-methoxy-phenyl)-nicotinamide	323.17	*
127.		6-(3-Fluoro-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide	335.21	*
128.		6-(3-Fluoro-phenyl)-N-(4-propyl-phenyl)-nicotinamide	335.21	
129.		6-(3-Fluoro-phenyl)-N-indan-5-yl-nicotinamide	333.21	*
130.		6-(3-Isopropyl-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide	388.25	*

	Compound	Name	(M+1)	K _i
131.		6-(3-Isopropyl-phenyl)-N-(3-methoxy-phenyl)-nicotinamide	347.24	*
132.		6-(3-Isopropyl-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide	402.32	
133.		6-(3-Methoxy-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide	376.21	
134.		6-(3-Methoxy-phenyl)-N-(4-propyl-phenyl)-nicotinamide	347.24	
135.		6-(3-Trifluoromethoxy-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide	427.19	*
136.		6-(4-Butyl-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide	402.28	
137.		6-(4-Butyl-phenyl)-N-(3-methoxy-phenyl)-nicotinamide	361.25	*
138.		6-(4-Butyl-phenyl)-N-(3-tert-butyl-phenyl)-nicotinamide	387.32	
139.		6-(4-Chloro-phenyl)-N-(3,4-dimethyl-phenyl)-nicotinamide	337.10	
140.		6-(4-Chloro-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide	341.07	

	Compound	Name	(M+1)	K _i
141.		6-(4-Chloro-phenyl)-N-indan-5-yl-nicotinamide	349.10	
142.		6-(4-Dimethylamino-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide	360.30	
143.		6-(4-Fluoro-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide	364.18	
144.		6-(4-Fluoro-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide	361.19	
145.		6-(4-Fluoro-phenyl)-N-indan-5-yl-nicotinamide	333.21	
146.		6-(4-Isopropyl-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide	388.25	
147.		6-(4-Isopropyl-phenyl)-N-(3-methoxy-phenyl)-nicotinamide	347.24	*
148.		6-(4-Isopropyl-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide	402.34	
149.		6-(5-Chloro-2-methoxy-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide	410.10	
150.		6-(5-Chloro-2-methoxy-phenyl)-N-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-nicotinamide	411.13	
151.		6-(5-Chloro-2-methoxy-phenyl)-N-(3,4-dimethyl-phenyl)-nicotinamide	367.13	

	Compound	Name	(M+1)	K _i
152.		6-(5-Chloro-2-methoxy-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide	371.10	
153.		6-(5-Chloro-2-methoxy-phenyl)-N-(3-methoxy-phenyl)-nicotinamide	369.11	
154.		6-(5-Chloro-2-methoxy-phenyl)-N-(4-chloro-phenyl)-nicotinamide	373.09	
155.		6-(5-Chloro-2-methoxy-phenyl)-N-(4-ethyl-phenyl)-nicotinamide	367.13	
156.		6-(5-Chloro-2-methoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide	381.14	
157.		6-(5-Chloro-2-methoxy-phenyl)-N-(4-propyl-phenyl)-nicotinamide	381.13	*
158.		6-(5-Chloro-2-methoxy-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide	407.12	
159.		6-(5-Chloro-2-methoxy-phenyl)-N-indan-5-yl-nicotinamide	379.13	
160.		6-(5-Fluoro-2-methoxy-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide	355.12	
161.		6-(5-Fluoro-2-methoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide	365.16	

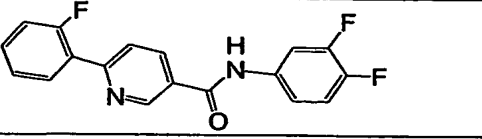
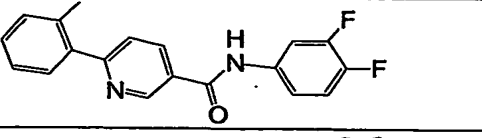
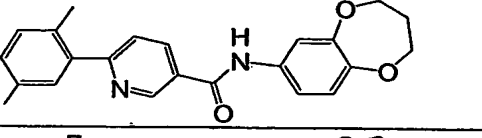
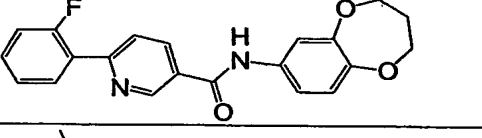
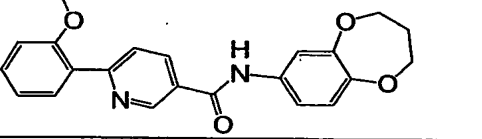
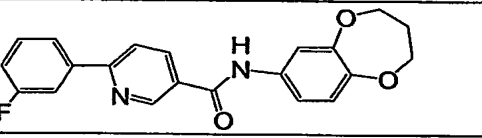
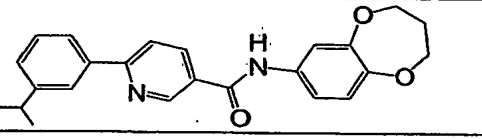
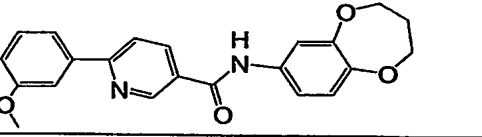
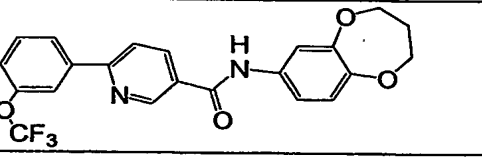
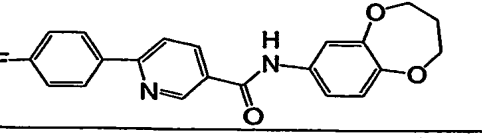
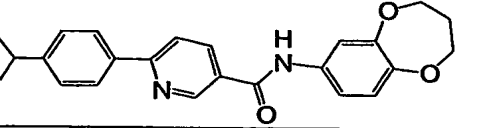
	Compound	Name	(M+1)	K _i
162.		6-(5-Fluoro-2-methoxy-phenyl)-N-(4-propyl-phenyl)-nicotinamide	365.16	
163.		6-(5-Fluoro-2-methoxy-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide	391.13	
164.		6-(5-Fluoro-2-methoxy-phenyl)-N-indan-5-yl-nicotinamide	363.15	
165.		6-(5-Isopropyl-2-methoxy-phenyl)-N-(3-methoxy-phenyl)-nicotinamide	377.19	
166.		6-(5-Isopropyl-2-methoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide	389.21	
167.		6-(5-Isopropyl-2-methoxy-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide	432.27	
168.		6,N-Bis-(3,4-dimethyl-phenyl)-nicotinamide	331.23	
169.		6-Benzo[1,3]dioxol-5-yl-N-(2-methyl-benzothiazol-5-yl)-nicotinamide	390.19	
170.		6-Benzo[1,3]dioxol-5-yl-N-(3,4-dimethyl-phenyl)-nicotinamide	347.21	
171.		6-Benzo[1,3]dioxol-5-yl-N-(3-methoxy-phenyl)-nicotinamide	349.19	

Compound	Name	(M+1)	K _i
172. 	6-Benzo[1,3]dioxol-5-yl-N-(3- <i>tert</i> -butyl-phenyl)-nicotinamide	375.24	
173. 	6-Benzo[1,3]dioxol-5-yl-N-(4-isopropyl-phenyl)-nicotinamide	361.24	
174. 	6-Biphenyl-3-yl-N-(3,4-dimethyl-phenyl)-nicotinamide	379.16	
175. 	6-Biphenyl-3-yl-N-indan-5-yl-nicotinamide	391.16	
176. 	6-Dibenzofuran-4-yl-N-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-nicotinamide	423.17	
177. 	6-Dibenzofuran-4-yl-N-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-nicotinamide	437.19	
178. 	6-Dibenzofuran-4-yl-N-(3,4-dimethyl-phenyl)-nicotinamide	393.16	
179. 	6-Dibenzofuran-4-yl-N-(3-methoxy-phenyl)-nicotinamide	395.17	
180. 	6-Dibenzofuran-4-yl-N-indan-5-yl-nicotinamide	405.17	
181. 	6-Methyl-3'-trifluoromethyl-[2,2']bipyridinyl-5-carboxylic acid (4-trifluoromethyl-phenyl)-amide	426.15	*

	Compound	Name	(M+1)	K _i
182.		6-m-Tolyl-N-(4-trifluoromethyl-phenyl)-nicotinamide	357.21	
183.		6-o-Tolyl-N-(2,3,4-trifluoro-phenyl)-nicotinamide	343.15	
184.		6-o-Tolyl-N-(3-trifluoromethyl-phenyl)-nicotinamide	357.17	
185.		6-o-Tolyl-N-(4-trifluoromethyl-phenyl)-nicotinamide	357.14	*
186.		6-o-Tolyl-N-p-tolyl-nicotinamide	303.19	
187.		6-Phenyl-N-(4-propyl-phenyl)-nicotinamide	317.18	
188.		6-Phenyl-N-(4-trifluoromethyl-phenyl)-nicotinamide		
189.		Biphenyl-4-carboxylic acid (4-chloro-3-methoxy-phenyl)-amide		*
190.		N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(2,5-dimethoxy-phenyl)-nicotinamide	393.16	
191.		N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(2,5-dimethyl-phenyl)-nicotinamide	361.17	
192.		N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(2-fluoro-phenyl)-nicotinamide	351.17	*

	Compound	Name	(M+1)	K _i
193.		N-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-6-(2-methoxy-phenyl)-nicotinamide	363.15	
194.		N-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-6-(3-ethoxy-phenyl)-nicotinamide	377.23	*
195.		N-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-6-(3-fluoro-phenyl)-nicotinamide	351.20	
196.		N-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-6-(3-isopropyl-phenyl)-nicotinamide	375.25	*
197.		N-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-6-(3-methoxy-phenyl)-nicotinamide	363.21	
198.		N-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-6-(3-trifluoromethoxy-phenyl)-nicotinamide	417.20	
199.		N-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-6-(4-isopropyl-phenyl)-nicotinamide	375.25	
200.		N-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide	381.15	
201.		N-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide	405.19	
202.		N-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-6-m-tolyl-nicotinamide	347.21	*
203.		N-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-6-o-tolyl-nicotinamide	347.15	

	Compound	Name	(M+1)	K _i
204.		N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-p-tolyl-nicotinamide	347.22	
205.		N-(2-Chloro-6-methyl-phenyl)-6-o-tolyl-nicotinamide	337.21	
206.		N-(2-Isopropyl-6-methyl-phenyl)-6-o-tolyl-nicotinamide	345.28	
207.		N-(2-Methyl-benzothiazol-5-yl)-6-(3-trifluoromethoxy-phenyl)-nicotinamide	430.19	*
208.		N-(2-Methyl-benzothiazol-5-yl)-6-m-tolyl-nicotinamide	360.21	*
209.		N-(2-Methyl-benzothiazol-5-yl)-6-phenyl-nicotinamide	346.18	*
210.		N-(2-Methyl-benzothiazol-5-yl)-6-p-tolyl-nicotinamide	360.20	
211.		N-(3,4-Dichloro-phenyl)-6-(2-fluoro-phenyl)-nicotinamide	361.11	
212.		N-(3,4-Dichloro-phenyl)-6-(2-methoxy-phenyl)-nicotinamide	373.13	
213.		N-(3,4-Dichloro-phenyl)-6-o-tolyl-nicotinamide	357.12	
214.		N-(3,4-Difluoro-phenyl)-4-(3-fluoro-pyridin-2-yl)-benzamide	329.12	*

	Compound	Name	(M+1)	K _i
215.		N-(3,4-Difluoro-phenyl)-6-(2-fluoro-phenyl)-nicotinamide	329.14	
216.		N-(3,4-Difluoro-phenyl)-6-o-tolyl-nicotinamide	325.15	
217.		N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(2,5-dimethyl-phenyl)-nicotinamide	375.18	
218.		N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(2-fluoro-phenyl)-nicotinamide	365.21	*
219.		N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(2-methoxy-phenyl)-nicotinamide	377.16	
220.		N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(3-fluoro-phenyl)-nicotinamide	365.21	*
221.		N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(3-isopropyl-phenyl)-nicotinamide	389.27	*
222.		N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(3-methoxy-phenyl)-nicotinamide	377.23	
223.		N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(3-trifluoromethoxy-phenyl)-nicotinamide	431.21	*
224.		N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(4-fluoro-phenyl)-nicotinamide	365.22	
225.		N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(4-isopropyl-phenyl)-nicotinamide	389.27	

	Compound	Name	(M+1)	K _i
226.		N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide	395.17	
227.		N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide	419.20	
228.		N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-m-tolyl-nicotinamide	361.23	
229.		N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-o-tolyl-nicotinamide	361.16	
230.		N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-phenyl-nicotinamide	347.21	*
231.		N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-p-tolyl-nicotinamide	361.23	
232.		N-(3,4-Dimethoxy-phenyl)-6-(2-fluoro-phenyl)-nicotinamide	351.19	*
233.		N-(3,4-Dimethyl-phenyl)-6-(2,5-dimethyl-phenyl)-nicotinamide	331.18	
234.		N-(3,4-Dimethyl-phenyl)-6-(2-fluoro-phenyl)-nicotinamide	321.20	
235.		N-(3,4-Dimethyl-phenyl)-6-(2-methoxy-phenyl)-nicotinamide	333.16	
236.		N-(3,4-Dimethyl-phenyl)-6-(2-methylsulfanyl-phenyl)-nicotinamide	349.14	

	Compound	Name	(M+1)	K _i
237.		N-(3,4-Dimethyl-phenyl)-6-(3,5-dimethyl-phenyl)-nicotinamide	331.23	*
238.		N-(3,4-Dimethyl-phenyl)-6-(3-ethoxy-phenyl)-nicotinamide	347.24	*
239.		N-(3,4-Dimethyl-phenyl)-6-(3-fluoro-phenyl)-nicotinamide	321.19	*
240.		N-(3,4-Dimethyl-phenyl)-6-(3-isopropyl-phenyl)-nicotinamide	345.25	
241.		N-(3,4-Dimethyl-phenyl)-6-(3-methoxy-phenyl)-nicotinamide	333.21	*
242.		N-(3,4-Dimethyl-phenyl)-6-(3-trifluoromethoxy-phenyl)-nicotinamide	387.21	*
243.		N-(3,4-Dimethyl-phenyl)-6-(3-trifluoromethyl-phenyl)-nicotinamide	371.11	
244.		N-(3,4-Dimethyl-phenyl)-6-(4-fluoro-phenyl)-nicotinamide	321.20	
245.		N-(3,4-Dimethyl-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide	351.15	
246.		N-(3,4-Dimethyl-phenyl)-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide	375.20	

	Compound	Name	(M+1)	K _i
247.		N-(3,4-Dimethyl-phenyl)-6-m-tolyl-nicotinamide	317.21	*
248.		N-(3,4-Dimethyl-phenyl)-6-o-tolyl-nicotinamide	317.17	*
249.		N-(3,4-Dimethyl-phenyl)-6-phenyl-nicotinamide	303.19	*
250.		N-(3,4-Dimethyl-phenyl)-6-p-tolyl-nicotinamide	317.21	
251.		N-(3,5-Bis-trifluoromethyl-phenyl)-6-(2-chloro-phenyl)-nicotinamide	445.16	
252.		N-(3,5-Bis-trifluoromethyl-phenyl)-6-(2-fluoro-phenyl)-nicotinamide	429.16	
253.		N-(3,5-Bis-trifluoromethyl-phenyl)-6-o-tolyl-nicotinamide	425.19	
254.		N-(3,5-Dichloro-phenyl)-6-(2-fluoro-phenyl)-nicotinamide	361.10	
255.		N-(3,5-Dichloro-phenyl)-6-o-tolyl-nicotinamide	357.12	
256.		N-(3-Chloro-4-morpholin-4-yl-phenyl)-6-(2-chloro-phenyl)-nicotinamide	428.24	
257.		N-(3-Chloro-4-morpholin-4-yl-phenyl)-6-(2-fluoro-phenyl)-nicotinamide	412.24	

	Compound	Name	(M+1)	K _i
258.		N-(3-Chloro-4-morpholin-4-yl-phenyl)-6-o-tolyl-nicotinamide	408.27	
259.		N-(3-Chloro-phenyl)-6-(2-chloro-phenyl)-nicotinamide	343.10	
260.		N-(3-Chloro-phenyl)-6-(2-fluoro-phenyl)-nicotinamide	327.12	
261.		N-(3-Chloro-phenyl)-6-o-tolyl-nicotinamide	323.13	
262.		N-(3-Cyclopentyloxy-4-methoxy-phenyl)-6-o-tolyl-nicotinamide	403.27	
263.		N-(3-Fluoro-4-methyl-phenyl)-6-(2-fluoro-phenyl)-nicotinamide	325.17	
264.		N-(3-Fluoro-4-methyl-phenyl)-6-(2-methoxy-phenyl)-nicotinamide	337.14	
265.		N-(3-Fluoro-4-methyl-phenyl)-6-(2-methylsulfanyl-phenyl)-nicotinamide	353.11	
266.		N-(3-Fluoro-4-methyl-phenyl)-6-(3-fluoro-phenyl)-nicotinamide	325.17	*
267.		N-(3-Fluoro-4-methyl-phenyl)-6-(3-isopropyl-phenyl)-nicotinamide	349.22	*

	Compound	Name	(M+1)	K _i
268.		N-(3-Fluoro-4-methyl-phenyl)-6-(3-methoxy-phenyl)-nicotinamide	337.19	*
269.		N-(3-Fluoro-4-methyl-phenyl)-6-(3-trifluoromethyl-phenyl)-nicotinamide	375.09	
270.		N-(3-Fluoro-4-methyl-phenyl)-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide	379.17	
271.		N-(3-Fluoro-4-methyl-phenyl)-6-m-tolyl-nicotinamide	321.19	
272.		N-(3-Fluoro-4-methyl-phenyl)-6-o-tolyl-nicotinamide	321.14	
273.		N-(3-Fluoro-4-methyl-phenyl)-6-phenyl-nicotinamide	307.18	
274.		N-(3-Fluoro-phenyl)-6-(2-fluorophenyl)-nicotinamide	311.13	
275.		N-(3-Fluoro-phenyl)-6-o-tolyl-nicotinamide	307.14	
276.		N-(3-Methoxy-phenyl)-6-(2-methoxy-phenyl)-nicotinamide	335.15	
277.		N-(3-Methoxy-phenyl)-6-(3,4,5-trimethoxy-phenyl)-nicotinamide	395.25	

	Compound	Name	(M+1)	K _i
278.		N-(3-Methoxy-phenyl)-6-(3-trifluoromethoxy-phenyl)-nicotinamide	389.19	*
279.		N-(3-Methoxy-phenyl)-6-(4-methoxy-phenyl)-nicotinamide	335.19	
280.		N-(3-Methoxy-phenyl)-6-m-tolyl-nicotinamide	319.19	*
281.		N-(3-Methoxy-phenyl)-6-o-tolyl-nicotinamide	319.15	
282.		N-(3-Methoxy-phenyl)-6-phenyl-nicotinamide	305.17	*
283.		N-(3-Methoxy-phenyl)-6-p-tolyl-nicotinamide	319.19	
284.		N-(3-Phenoxy-phenyl)-6-o-tolyl-nicotinamide	381.26	
285.		N-(3-tert-Butyl-phenyl)-6-(2,4-difluoro-phenyl)-nicotinamide	367.13	
286.		N-(3-tert-Butyl-phenyl)-6-(2,5-dimethyl-phenyl)-nicotinamide	359.20	
287.		N-(3-tert-Butyl-phenyl)-6-(2-chloro-phenyl)-nicotinamide	365.22	

	Compound	Name	(M+1)	K _i
288.		N-(3- <i>tert</i> -Butyl-phenyl)-6-(2-fluoro-phenyl)-nicotinamide	349.23	*
289.		N-(3- <i>tert</i> -Butyl-phenyl)-6-(2-methoxy-phenyl)-nicotinamide	361.19	
290.		N-(3- <i>tert</i> -Butyl-phenyl)-6-(2-methylsulfanyl-phenyl)-nicotinamide	377.16	
291.		N-(3- <i>tert</i> -Butyl-phenyl)-6-(3,4,5-trimethoxy-phenyl)-nicotinamide	421.31	
292.		N-(3- <i>tert</i> -Butyl-phenyl)-6-(3,4-difluoro-phenyl)-nicotinamide	367.13	
293.		N-(3- <i>tert</i> -Butyl-phenyl)-6-(3,4-dimethyl-phenyl)-nicotinamide	359.28	
294.		N-(3- <i>tert</i> -Butyl-phenyl)-6-(3-chloro-phenyl)-nicotinamide	365.12	
295.		N-(3- <i>tert</i> -Butyl-phenyl)-6-(3-cyano-phenyl)-nicotinamide	356.15	
296.		N-(3- <i>tert</i> -Butyl-phenyl)-6-(3-fluoro-phenyl)-nicotinamide	349.23	*
297.		N-(3- <i>tert</i> -Butyl-phenyl)-6-(3-isopropyl-phenyl)-nicotinamide	373.30	

	Compound	Name	(M+1)	K _i
298.		N-(3- <i>tert</i> -Butyl-phenyl)-6-(3-methoxy-phenyl)-nicotinamide	361.25	
299.		N-(3- <i>tert</i> -Butyl-phenyl)-6-(3-trifluoromethyl-phenyl)-nicotinamide	399.14	
300.		N-(3- <i>tert</i> -Butyl-phenyl)-6-(4-chloro-phenyl)-nicotinamide	365.12	
301.		N-(3- <i>tert</i> -Butyl-phenyl)-6-(4-trifluoromethoxy-phenyl)-nicotinamide	415.25	
302.		N-(3- <i>tert</i> -Butyl-phenyl)-6-(5-chloro-2-methoxy-phenyl)-nicotinamide	395.15	
303.		N-(3- <i>tert</i> -Butyl-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide	379.19	
304.		N-(3- <i>tert</i> -Butyl-phenyl)-6-p-tolyl-nicotinamide	345.26	
305.		N-(4-Bromo-2-fluoro-phenyl)-6-o-tolyl-nicotinamide	385.12	
306.		N-(4-Bromo-3-chloro-phenyl)-6-(2,4-dimethoxy-phenyl)-nicotinamide	449.06	
307.		N-(4-Bromo-3-chloro-phenyl)-6-(2,5-dimethoxy-phenyl)-nicotinamide	449.06	

	Compound	Name	(M+1)	K _i
308.		N-(4-Bromo-3-chloro-phenyl)-6-(2,5-dimethyl-phenyl)-nicotinamide	417.06	
309.		N-(4-Bromo-3-chloro-phenyl)-6-(2,6-dimethoxy-phenyl)-nicotinamide	449.06	
310.		N-(4-Bromo-3-chloro-phenyl)-6-(2-chloro-phenyl)-nicotinamide	423.05	
311.		N-(4-Bromo-3-chloro-phenyl)-6-(2-fluoro-phenyl)-nicotinamide	407.09	
312.		N-(4-Bromo-3-chloro-phenyl)-6-(2-methoxy-phenyl)-nicotinamide	419.04	
313.		N-(4-Bromo-3-chloro-phenyl)-6-(2-methylsulfanyl-phenyl)-nicotinamide	435.03	
314.		N-(4-Bromo-3-chloro-phenyl)-6-(3,4,5-trimethoxy-phenyl)-nicotinamide	479.16	
315.		N-(4-Bromo-3-chloro-phenyl)-6-(3,4-dimethoxy-phenyl)-nicotinamide	449.15	
316.		N-(4-Bromo-3-chloro-phenyl)-6-(3,5-dimethyl-phenyl)-nicotinamide	417.14	*
317.		N-(4-Bromo-3-chloro-phenyl)-6-(3-ethoxy-phenyl)-nicotinamide	433.14	*

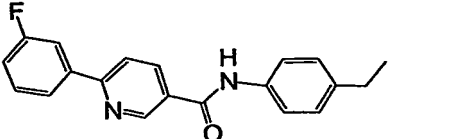
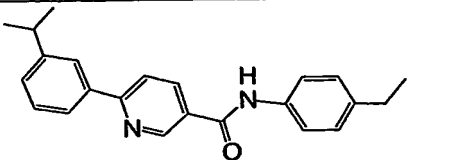
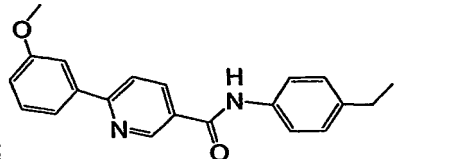
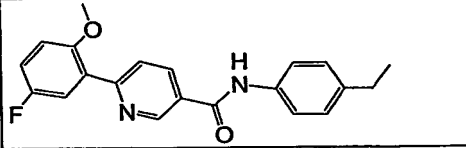
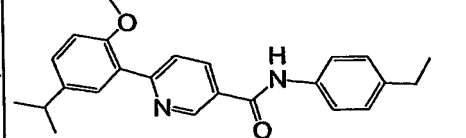
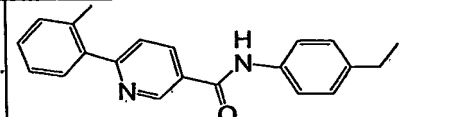
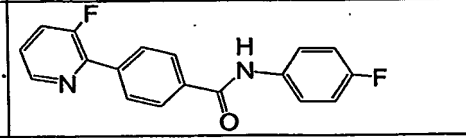
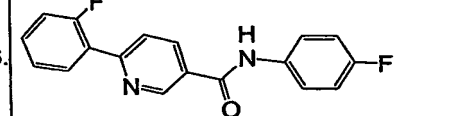
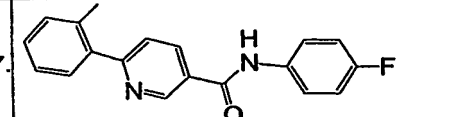
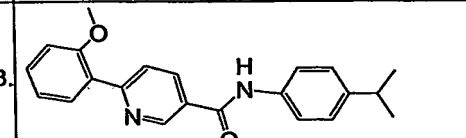
	Compound	Name	(M+1)	K _i
318.		N-(4-Bromo-3-chloro-phenyl)-6-(3-fluoro-phenyl)-nicotinamide	407.10	*
319.		N-(4-Bromo-3-chloro-phenyl)-6-(3-methoxy-phenyl)-nicotinamide	419.12	
320.		N-(4-Bromo-3-chloro-phenyl)-6-(4-fluoro-phenyl)-nicotinamide	407.10	*
321.		N-(4-Bromo-3-chloro-phenyl)-6-(4-isopropyl-phenyl)-nicotinamide	431.17	*
322.		N-(4-Bromo-3-chloro-phenyl)-6-(4-trifluoromethoxy-phenyl)-nicotinamide	473.11	
323.		N-(4-Bromo-3-chloro-phenyl)-6-(5-chloro-2-methoxy-phenyl)-nicotinamide	453.02	
324.		N-(4-Bromo-3-chloro-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide	437.04	
325.		N-(4-Bromo-3-chloro-phenyl)-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide	461.08	
326.		N-(4-Bromo-3-chloro-phenyl)-6-m-tolyl-nicotinamide	403.12	
327.		N-(4-Bromo-3-chloro-phenyl)-6-o-tolyl-nicotinamide	403.04	

	Compound	Name	(M+1)	K _i
328.		N-(4-Bromo-3-chloro-phenyl)-6-phenyl-nicotinamide	389.10	
329.		N-(4-Bromo-3-chloro-phenyl)-6-p-tolyl-nicotinamide	403.12	
330.		N-(4-Bromo-3-trifluoromethyl-phenyl)-6-(2-fluoro-phenyl)-nicotinamide		
331.		N-(4-Bromo-3-trifluoromethyl-phenyl)-6-(2-methoxy-phenyl)-nicotinamide		
332.		N-(4-Butyl-phenyl)-4-(3-chloro-pyridin-2-yl)-benzamide	365.16	*
333.		N-(4-Butyl-phenyl)-6-(2,4-dimethoxy-phenyl)-nicotinamide	391.20	
334.		N-(4-Butyl-phenyl)-6-(2,5-dimethyl-phenyl)-nicotinamide	359.20	
335.		N-(4-Butyl-phenyl)-6-(2,6-dimethoxy-phenyl)-nicotinamide	391.20	
336.		N-(4-Butyl-phenyl)-6-(2-chloro-phenyl)-nicotinamide	365.23	
337.		N-(4-Butyl-phenyl)-6-(2-fluoro-phenyl)-nicotinamide	349.22	
338.		N-(4-Butyl-phenyl)-6-(2-methoxy-phenyl)-nicotinamide	361.17	

	Compound	Name	(M+1)	K _i
339.		N-(4-Butyl-phenyl)-6-(2-methylsulfanyl-phenyl)-nicotinamide	377.16	
340.		N-(4-Butyl-phenyl)-6-(3-methoxy-phenyl)-nicotinamide	361.27	
341.		N-(4-Butyl-phenyl)-6-(5-chloro-2-methoxy-phenyl)-nicotinamide	395.15	
342.		N-(4-Butyl-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide	379.18	
343.		N-(4-Butyl-phenyl)-6-o-tolyl-nicotinamide	345.19	*
344.		N-(4-Chloro-naphthalen-1-yl)-6-o-tolyl-nicotinamide	373.21	
345.		N-(4-Chloro-phenyl)-6-(2,4-dimethoxy-phenyl)-nicotinamide	369.13	
346.		N-(4-Chloro-phenyl)-6-(2,5-dimethyl-phenyl)-nicotinamide	337.14	
347.		N-(4-Chloro-phenyl)-6-(2-chloro-phenyl)-nicotinamide	343.10	
348.		N-(4-Chloro-phenyl)-6-(2-fluoro-phenyl)-nicotinamide	327.13	*

	Compound	Name	(M+1)	K _i
349.		N-(4-Chloro-phenyl)-6-(2-methoxy-phenyl)-nicotinamide	339.11	
350.		N-(4-Chloro-phenyl)-6-(2-methylsulfanyl-phenyl)-nicotinamide	355.10	
351.		N-(4-Chloro-phenyl)-6-(3,4-dimethyl-phenyl)-nicotinamide	337.19	
352.		N-(4-Chloro-phenyl)-6-(3,5-dimethyl-phenyl)-nicotinamide	337.19	
353.		N-(4-Chloro-phenyl)-6-(3-ethoxy-phenyl)-nicotinamide	353.18	
354.		N-(4-Chloro-phenyl)-6-(3-fluoro-phenyl)-nicotinamide	327.14	
355.		N-(4-Chloro-phenyl)-6-(3-isopropyl-phenyl)-nicotinamide	351.20	
356.		N-(4-Chloro-phenyl)-6-(3-methoxy-phenyl)-nicotinamide	339.16	
357.		N-(4-Chloro-phenyl)-6-(4-fluoro-phenyl)-nicotinamide		
358.		N-(4-Chloro-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide	357.11	

	Compound	Name	(M+1)	K _i
359.		N-(4-Chloro-phenyl)-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide	381.17	
360.		N-(4-Chloro-phenyl)-6-dibenzofuran-4-yl-nicotinamide	399.14	
361.		N-(4-Chloro-phenyl)-6-m-tolyl-nicotinamide	323.16	
362.		N-(4-Chloro-phenyl)-6-o-tolyl-nicotinamide	323.12	
363.		N-(4-Cyclopentyl-phenyl)-4-(3-fluoro-pyridin-2-yl)-benzamide	361.20	*
364.		N-(4-Difluoromethoxy-phenyl)-6-o-tolyl-nicotinamide	355.17	
365.		N-(4-Ethyl-phenyl)-6-(2-fluoro-phenyl)-nicotinamide	321.18	*
366.		N-(4-Ethyl-phenyl)-6-(2-methoxy-phenyl)-nicotinamide	333.15	
367.		N-(4-Ethyl-phenyl)-6-(2-methylsulfanyl-phenyl)-nicotinamide	349.13	
368.		N-(4-Ethyl-phenyl)-6-(3,4,5-trimethoxy-phenyl)-nicotinamide	393.28	

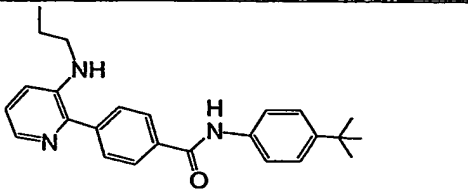
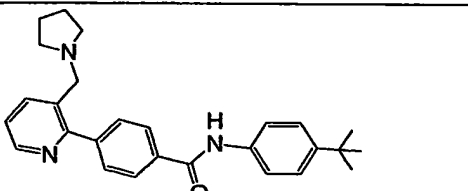
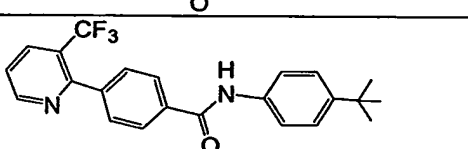
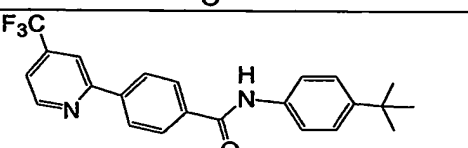
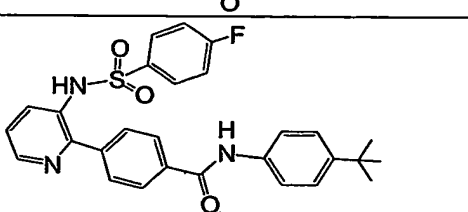
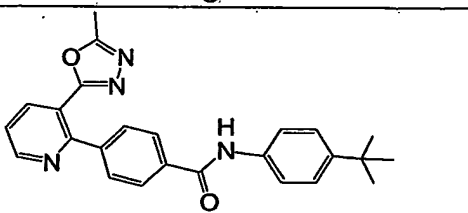
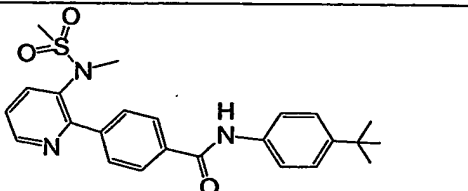
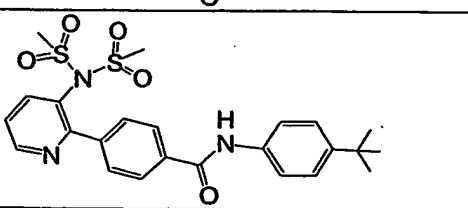
	Compound	Name	(M+1)	K _i
369.		N-(4-Ethyl-phenyl)-6-(3-fluoro-phenyl)-nicotinamide	321.19	
370.		N-(4-Ethyl-phenyl)-6-(3-isopropyl-phenyl)-nicotinamide	345.24	
371.		N-(4-Ethyl-phenyl)-6-(3-methoxy-phenyl)-nicotinamide	333.22	
372.		N-(4-Ethyl-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide	351.14	
373.		N-(4-Ethyl-phenyl)-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide	375.20	
374.		N-(4-Ethyl-phenyl)-6-o-tolyl-nicotinamide	317.17	*
375.		N-(4-Fluoro-phenyl)-4-(3-fluoro-pyridin-2-yl)-benzamide	311.13	*
376.		N-(4-Fluoro-phenyl)-6-(2-fluoro-phenyl)-nicotinamide	311.14	
377.		N-(4-Fluoro-phenyl)-6-o-tolyl-nicotinamide	307.15	
378.		N-(4-Isopropyl-phenyl)-6-(2-methoxy-phenyl)-nicotinamide	347.17	*

	Compound	Name	(M+1)	K _i
379.		N-(4-Isopropyl-phenyl)-6-(2-methylsulfanyl-phenyl)-nicotinamide	363.15	
380.		N-(4-Isopropyl-phenyl)-6-(3,4,5-trimethoxy-phenyl)-nicotinamide	407.30	
381.		N-(4-Isopropyl-phenyl)-6-(3-isopropyl-phenyl)-nicotinamide	359.26	
382.		N-(4-Isopropyl-phenyl)-6-(3-trifluoromethoxy-phenyl)-nicotinamide	401.25	
383.		N-(4-Isopropyl-phenyl)-6-m-tolyl-nicotinamide	331.22	*
384.		N-(4-Isopropyl-phenyl)-6-o-tolyl-nicotinamide	331.18	*
385.		N-(4-Isopropyl-phenyl)-6-phenyl-nicotinamide	317.19	*
386.		N-(4-Morpholin-4-yl-phenyl)-6-m-tolyl-nicotinamide	374.29	
387.		N-(4-Morpholin-4-yl-phenyl)-6-o-tolyl-nicotinamide	374.22	
388.		N-(4-Morpholin-4-yl-phenyl)-6-phenyl-nicotinamide		
389.		N-(4-Propyl-phenyl)-6-o-tolyl-nicotinamide	331.17	*

	Compound	Name	(M+1)	K _i
390.		N-(4-sec-Butyl-phenyl)-4-(3-fluoro-pyridin-2-yl)-benzamide	349.20	*
391.		N-(4-tert-Butyl-2-chloro-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide	413.15	*
392.		N-(4-tert-Butyl-cyclohexyl)-4-(3-chloro-pyridin-2-yl)-benzamide (trans)	371.2	*
393.		N-(4-tert-Butyl-cyclohexyl)-4-(3-chloro-pyridin-2-yl)-benzamide (cis)	371.2	*
394.		N-(4-tert-Butyl-phenyl)-2-hydroxy-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide	493.10	*
395.		N-(4-tert-Butyl-phenyl)-2-nitro-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide	522.12	*
396.		N-(4-tert-Butyl-phenyl)-4-(1H-indol-5-yl)-benzamide	369.22	*
397.		N-(4-tert-Butyl-phenyl)-4-(1-methanesulfonyl-piperidin-2-yl)-benzamide	415.2	*
398.		N-(4-tert-Butyl-phenyl)-4-(1-methyl-piperidin-2-yl)-benzamide	351.3	*
399.		N-(4-tert-Butyl-phenyl)-4-(1-propyl-piperidin-2-yl)-benzamide	379.3	*
400.		N-(4-tert-Butyl-phenyl)-4-(3,5-dichloro-pyridin-2-yl)-benzamide	399.14	*

	Compound	Name	(M+1)	K _i
401.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-[1,3,4]oxadiazol-2-yl-pyridin-2-yl)-benzamide	399.22	*
402.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-benzamide	433.18	*
403.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-chloro-pyrazin-2-yl)-benzamide	366.20	*
404.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-chloro-pyridin-2-yl)-benzamide	365.16	*
405.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-cyano-pyridin-2-yl)-benzamide	356.19	*
406.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-cyclopentylamino-pyridin-2-yl)-benzamide	414.26	*
407.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-dimethylaminomethyl-pyridin-2-yl)-benzamide	388.27	*
408.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-ethanesulfonylamino-pyridin-2-yl)-benzamide	438.23	*
409.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-fluoro-pyridin-2-yl)-benzamide	349.18	*

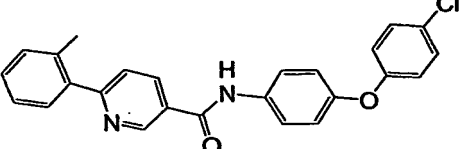
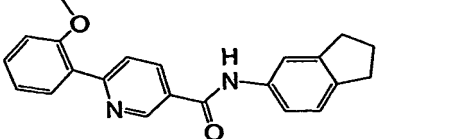
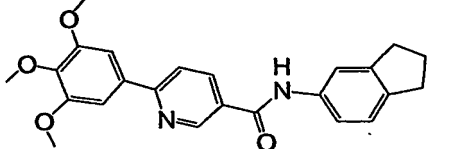
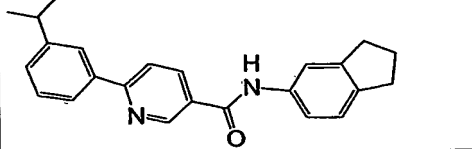
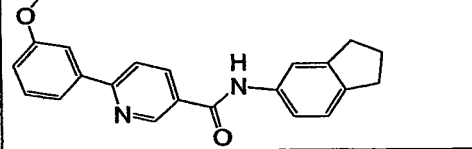
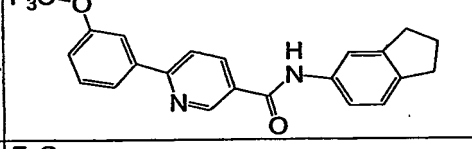
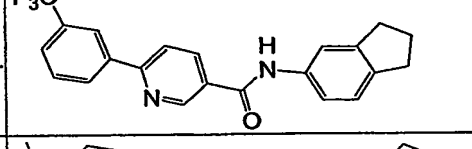
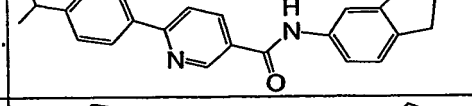
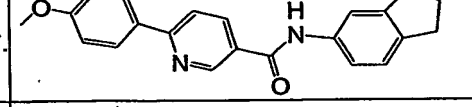
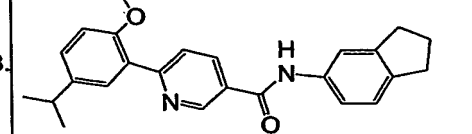
	Compound	Name	(M+1)	K _i
410.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-formyl-pyridin-2-yl)-benzamide	359.21	*
411.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-hydroxyamino-pyridin-2-yl)-benzamide		*
412.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-hydroxymethyl-pyridin-2-yl)-benzamide	361.22	*
413.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-methanesulfonylamino-pyridin-2-yl)-benzamide	424.19	*
414.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-methyl-pyridin-2-yl)-benzamide	345.22	*
415.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-nitro-pyridin-2-yl)-benzamide	376.18	*
416.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-nitro-pyridin-4-yl)-benzamide	376.23	*
417.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-phenylmethanesulfonylamino-pyridin-2-yl)-benzamide	500.24	*
418.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-propoxy-pyridin-2-yl)-benzamide	389.22	*

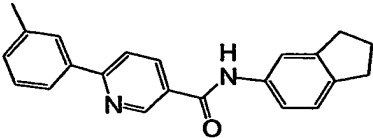
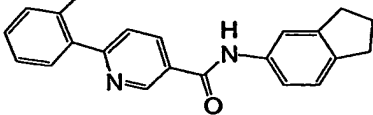
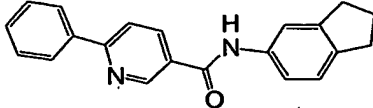
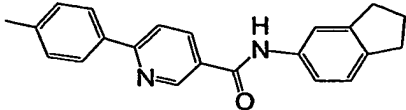
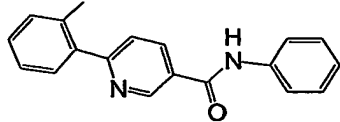
	Compound	Name	(M+1)	K _i
419.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-propylamino-pyridin-2-yl)-benzamide	388.24	*
420.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-pyrrolidin-1-ylmethyl-pyridin-2-yl)-benzamide	414.29	*
421.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(3-(trifluoromethyl)-pyridin-2-yl)-benzamide	399.20	*
422.		N-(4- <i>tert</i> -Butyl-phenyl)-4-(4-(trifluoromethyl)-pyridin-2-yl)-benzamide	399.18	*
423.		N-(4- <i>tert</i> -Butyl-phenyl)-4-[3-(4-fluorobenzenesulfonylamino)-pyridin-2-yl]-benzamide	504.22	*
424.		N-(4- <i>tert</i> -Butyl-phenyl)-4-[3-(5-methyl-[1,3,4]oxadiazol-2-yl)-pyridin-2-yl]-benzamide	413.21	*
425.		N-(4- <i>tert</i> -Butyl-phenyl)-4-[3-(methanesulfonylmethyl-amino)-pyridin-2-yl]-benzamide	438.21	*
426.		N-(4- <i>tert</i> -Butyl-phenyl)-4-[3-(N,N-dimethanesulfonylamino)-pyridin-2-yl]-benzamide	502.19	*

	Compound	Name	(M+1)	K _i
427.		N-(4- <i>tert</i> -Butyl-phenyl)-4-[3-(N,N-dimethanesulfonyl)amino-pyridin-4-yl]-benzamide	502.23	*
428.		N-(4- <i>tert</i> -Butyl-phenyl)-4-[3-(toluene-4-sulfonylamino)-pyridin-2-yl]-benzamide	500.25	*
429.		N-(4- <i>tert</i> -Butyl-phenyl)-4-piperidin-2-yl-benzamide	337.3	*
430.		N-(4- <i>tert</i> -Butyl-phenyl)-4-pyridin-2-yl-benzamide	331.19	*
431.		N-(4- <i>tert</i> -Butyl-phenyl)-4-pyridin-3-yl-benzamide	331.21	*
432.		N-(4- <i>tert</i> -Butyl-phenyl)-4-pyridin-4-yl-benzamide	331.20	*
433.		N-(4- <i>tert</i> -Butyl-phenyl)-4-pyrimidin-2-yl-benzamide	332.20	*
434.		N-(4- <i>tert</i> -Butyl-phenyl)-4-quinolin-3-yl-benzamide	381.21	*
435.		N-(4- <i>tert</i> -Butyl-phenyl)-5-chloro-6-(2-chloro-phenyl)-nicotinamide	399.16	*
436.		N-(4- <i>tert</i> -Butyl-phenyl)-5-chloro-6-phenyl-nicotinamide	365.19	*
437.		N-(4- <i>tert</i> -Butyl-phenyl)-6-(2,4-difluoro-phenyl)-nicotinamide	367.19	*

	Compound	Name	(M+1)	K _i
438.		N-(4- <i>tert</i> -Butyl-phenyl)-6-(2,6-difluoro-phenyl)-nicotinamide	367.19	*
439.		N-(4- <i>tert</i> -Butyl-phenyl)-6-(2,6-dimethyl-phenyl)-nicotinamide		*
440.		N-(4- <i>tert</i> -Butyl-phenyl)-6-(2-chloro-4-ethoxy-phenyl)-nicotinamide	409.19	*
441.		N-(4- <i>tert</i> -Butyl-phenyl)-6-(2-chloro-phenyl)-4-hydroxy-nicotinamide	381.17	*
442.		N-(4- <i>tert</i> -Butyl-phenyl)-6-(2-chloro-phenyl)-nicotinamide	365.18	*
443.		N-(4- <i>tert</i> -Butyl-phenyl)-6-(2-fluoro-phenyl)-nicotinamide	349.19	*
444.		N-(4- <i>tert</i> -Butyl-phenyl)-6-(2-hydroxymethyl-phenyl)-nicotinamide	361.22	*
445.		N-(4- <i>tert</i> -Butyl-phenyl)-6-(2-methanesulfonylamino-phenyl)-nicotinamide	424.19	*
446.		N-(4- <i>tert</i> -Butyl-phenyl)-6-(2-nitro-phenyl)-nicotinamide	376.18	*
447.		N-(4- <i>tert</i> -Butyl-phenyl)-6-(2-trifluoromethyl-phenyl)-nicotinamide	399.21	*
448.		N-(4- <i>tert</i> -Butyl-phenyl)-6-(3-fluoro-phenyl)-nicotinamide	349.20	*

	Compound	Name	(M+1)	K _i
449.		N-(4- <i>tert</i> -Butyl-phenyl)-6-(3-methoxy-phenyl)-nicotinamide	373.21	
450.		N-(4- <i>tert</i> -Butyl-phenyl)-6-(4-hydroxy-phenyl)-nicotinamide	347.20	*
451.		N-(4- <i>tert</i> -Butyl-phenyl)-6-[2-(N,N-dimethanesulfonyl)amino-phenyl]-nicotinamide	502.18	*
452.		N-(4- <i>tert</i> -Butyl-phenyl)-6-m-tolyl-nicotinamide	345.26	*
453.		N-(4- <i>tert</i> -Butyl-phenyl)-6-o-tolyl-nicotinamide	345.20	*
454.		N-(4- <i>tert</i> -Butyl-phenyl)-6-phenyl-nicotinamide	661.59	*
455.		N-(4-Trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide	489.03	*
456.		N-(4-Trifluoromethyl-phenyl)-4-[3-(N,N-dimethanesulfonyl)amino-pyridin-2-yl]-benzamide	514.11	*
457.		N-(5-Trifluoromethyl-pyridin-2-yl)-4-[3-(N,N-dimethanesulfonyl)amino-pyridin-2-yl]-benzamide	515.11	*
458.		N-[4-(3-Ethyl-2,6-dioxo-piperidin-3-yl)-phenyl]-4-(3-fluoro-pyridin-2-yl)-benzamide	432.22	*

	Compound	Name	(M+1)	K _i
459.		N-[4-(4-Chloro-phenoxy)-phenyl]-6-o-tolyl-nicotinamide	415.20	*
460.		N-Indan-5-yl-6-(2-methoxy-phenyl)-nicotinamide	345.17	
461.		N-Indan-5-yl-6-(3,4,5-trimethoxy-phenyl)-nicotinamide	405.28	
462.		N-Indan-5-yl-6-(3-isopropyl-phenyl)-nicotinamide	357.26	*
463.		N-Indan-5-yl-6-(3-methoxy-phenyl)-nicotinamide	345.22	*
464.		N-Indan-5-yl-6-(3-trifluoromethoxy-phenyl)-nicotinamide	399.23	
465.		N-Indan-5-yl-6-(3-trifluoromethyl-phenyl)-nicotinamide	383.12	
466.		N-Indan-5-yl-6-(4-isopropyl-phenyl)-nicotinamide	357.27	
467.		N-Indan-5-yl-6-(4-methoxy-phenyl)-nicotinamide	345.24	
468.		N-Indan-5-yl-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide	387.21	

	Compound	Name	(M+1)	K _i
469.		N-Indan-5-yl-6-m-tolyl-nicotinamide	329.22	
470.		N-Indan-5-yl-6-o-tolyl-nicotinamide	329.17	*
471.		N-Indan-5-yl-6-phenyl-nicotinamide	315.20	*
472.		N-Indan-5-yl-6-p-tolyl-nicotinamide	329.23	
473.		N-Phenyl-6-o-tolyl-nicotinamide	289.16	

EXAMPLE 4

VR1-TRANSFECTED CELLS AND MEMBRANE PREPARATIONS

This Example illustrates the preparation of VR1-transfected cells and membrane preparations for use in binding assays (Example 5) and functional assays (Example 6).

- 5 A cDNA encoding full length human capsaicin receptor (SEQ ID NO:1, 2 or 3 of U.S. Patent No. 6,482,611) was subcloned in the plasmid pBK-CMV (Stratagene, La Jolla, CA) for recombinant expression in mammalian cells.

Human embryonic kidney (HEK293) cells were transfected with the pBK-CMV expression construct encoding the full length human capsaicin receptor using standard
10 methods. The transfected cells were selected for two weeks in media containing G418 (400 µg/ml) to obtain a pool of stably transfected cells. Independent clones were isolated from this pool by limiting dilution to obtain clonal stable cell lines for use in subsequent experiments.

For radioligand binding experiments, cells were seeded in T175 cell culture flasks in
15 media without antibiotics and grown to approximately 90% confluency. The flasks were then washed with PBS and harvested in PBS containing 5 mM EDTA. The cells were pelleted by gentle centrifugation and stored at -80°C until assayed.

Previously frozen cells were disrupted with the aid of a tissue homogenizer in ice-cold HEPES homogenization buffer (5mM KCl, 5.8mM NaCl, 0.75mM CaCl₂, 2mM MgCl₂, 320 mM sucrose, and 10 mM HEPES pH 7.4). Tissue homogenates were first centrifuged for 10 minutes at 1000 x g (4°C) to remove the nuclear fraction and debris, and then the supernatant from the first centrifugation is further centrifuged for 30 minutes at 35,000 x g (4°C) to obtain a partially purified membrane fraction. Membranes were resuspended in the HEPES homogenization buffer prior to the assay. An aliquot of this membrane homogenate is used to determine protein concentration via the Bradford method (BIO-RAD Protein Assay Kit, #500-0001, BIO-RAD, Hercules, CA).

10

EXAMPLE 5

CAPSAICIN RECEPTOR BINDING ASSAY

This Example illustrates a representative assay of capsaicin receptor binding that may be used to determine the binding affinity of compounds for the capsaicin (VR1) receptor.

15 Binding studies with [³H] Resiniferatoxin (RTX) are carried out essentially as described by Szallasi and Blumberg (1992) *J. Pharmacol. Exp. Ther.* 262:883-888. In this protocol, non-specific RTX binding is reduced by adding bovine alpha₁ acid glycoprotein (100 µg per tube) after the binding reaction has been terminated.

[³H] RTX (37 Ci/mmol) is synthesized by and obtained from the Chemical Synthesis and Analysis Laboratory, National Cancer Institute-Frederick Cancer Research and Development Center, Frederick, MD. [³H] RTX may also be obtained from commercial vendors (e.g., Amersham Pharmacia Biotech, Inc.; Piscataway, NJ).

20 The membrane homogenate of Example 4 is centrifuged as before and resuspended to a protein concentration of 333µg/ml in homogenization buffer. Binding assay mixtures are set up on ice and contain [³H]RTX (specific activity 2200 mCi/ml), 2 µl non-radioactive test compound, 0.25 mg/ml bovine serum albumin (Cohn fraction V), and 5×10^4 - 1×10^5 VR1-transfected cells. The final volume is adjusted to 500 µl (for competition binding assays) or 1,000 µl (for saturation binding assays) with the ice-cold HEPES homogenization buffer solution (pH 7.4) described above. Non-specific binding is defined as that occurring in the presence of 1 µM non-radioactive RTX (Alexis Corp.; San Diego, CA). For saturation binding, [³H]RTX is added in the concentration range of 7 - 1,000 pM, using 1 to 2 dilutions. Typically 11 concentration points are collected per saturation binding curve.

30

Competition binding assays are performed in the presence of 60 pM [3 H]RTX and various concentrations of test compound. The binding reactions are initiated by transferring the assay mixtures into a 37°C water bath and are terminated following a 60 minute incubation period by cooling the tubes on ice. Membrane-bound RTX is separated from free, as well as any α_1 -acid glycoprotein-bound RTX, by filtration onto WALLAC glass fiber filters (PERKIN-ELMER, Gaithersburg, MD) which were pre-soaked with 1.0% PEI (polyethyleneimine) for 2 hours prior to use. Filters are allowed to dry overnight then counted in a WALLAC 1205 BETA PLATE counter after addition of WALLAC BETA SCINT scintillation fluid.

Equilibrium binding parameters are determined by fitting the allosteric Hill equation to the measured values with the aid of the computer program FIT P (Biosoft, Ferguson, MO) as described by Szallasi, *et al.* (1993) *J. Pharmacol. Exp. Ther.* 266:678-683. Compounds provided herein generally exhibit K_i values for capsaicin receptor of less than 1 μ M, 100 nM, 50 nM, 25 nM, 10 nM, or 1 nM in this assay.

EXAMPLE 6

CALCIUM MOBILIZATION ASSAY

This Example illustrates representative calcium mobilization assays for use in evaluating test compounds for agonist and antagonist activity.

Cells transfected with expression plasmids (as described in Example 4) and thereby expressing human capsaicin receptor are seeded and grown to 70-90% confluency in FALCON black-walled, clear-bottomed 96-well plates (#3904, BECTON-DICKINSON, Franklin Lakes, NJ). The culture medium is emptied from the 96 well plates and FLUO-3 AM calcium sensitive dye (Molecular Probes, Eugene, OR) is added to each well (dye solution: 1 mg FLUO-3 AM, 440 μ L DMSO and 440 μ L 20% pluronic acid in DMSO, diluted 1:250 in Krebs-Ringer HEPES (KRH) buffer (25 mM HEPES, 5 mM KCl, 0.96 mM NaH_2PO_4 , 1 mM MgSO_4 , 2 mM CaCl_2 , 5 mM glucose, 1 mM probenecid, pH 7.4), 50 μ L diluted solution per well). Plates are covered with aluminum foil and incubated at 37°C for 1-2 hours in an environment containing 5% CO_2 . After the incubation, the dye is emptied from the plates, and the cells are washed once with KRH buffer, and resuspended in KRH buffer.

DETERMINATION CAPSAICIN EC₅₀

To measure the ability of a test compound to agonize or antagonize a calcium mobilization response in cells expressing capsaicin receptors to capsaicin or other vanilloid agonist, the EC₅₀ of the agonist capsaicin is first determined. An additional 20 µl of KRH buffer and 1 µl DMSO is added to each well of cells, prepared as described above. 100 µl capsaicin in KRH buffer is automatically transferred by the FLIPR instrument to each well. Capsaicin-induced calcium mobilization is monitored using either FLUOROSKAN ASCENT (Labsystems; Franklin, MA) or FLIPR (fluorometric imaging plate reader system; Molecular Devices, Sunnyvale, CA) instruments. Data obtained between 30 and 60 seconds after agonist application are used to generate an 8-point concentration response curve, with final capsaicin concentrations of 1 nM to 3 µM. KALEIDAGRAPH software (Synergy Software, Reading, PA) is used to fit the data to the equation:

$$y=a*(1/(1+(b/x)^c))$$

to determine the 50% excitatory concentration (EC₅₀) for the response. In this equation, y is the maximum fluorescence signal, x is the concentration of the agonist or antagonist (in this case, capsaicin), a is the E_{max}, b corresponds to the EC₅₀ value and c is the Hill coefficient.

DETERMINATION OF AGONIST ACTIVITY

Test compounds are dissolved in DMSO, diluted in KRH buffer, and immediately added to cells prepared as described above. 100 nM capsaicin (an approximate EC₉₀ concentration) is also added to cells in the same 96-well plate as a positive control. The final concentration of test compounds in the assay wells is between 0.1 nM and 5 µM.

The ability of a test compound to act as an agonist of the capsaicin receptor is determined by measuring the fluorescence response of cells expressing capsaicin receptors elicited by the compound as function of compound concentration. This data is fit as described above to obtain the EC₅₀, which is generally less than 1 micromolar, preferably less than 100 nM, and more preferably less than 10 nM. The extent of efficacy of each test compound is also determined by calculating the response elicited by a concentration of test compound (typically 1 µM) relative to the response elicited by 100 nM capsaicin. This value, called Percent of Signal (POS), is calculated by the following equation:

$$POS=100*\text{test compound response} / 100 \text{ nM capsaicin response}$$

This analysis provides quantitative assessment of both the potency and efficacy of test compounds as human capsaicin receptor agonists. Agonists of the human capsaicin receptor generally elicit detectable responses at concentrations less than 100 µM, or preferably at

concentrations less than 1 μM , or most preferably at concentrations less than 10 nM. Extent of efficacy at human capsaicin receptor is preferably greater than 30 POS, more preferably greater than 80 POS at a concentration of 1 μM . Certain agonists are essentially free of antagonist activity as demonstrated by the absence of detectable antagonist activity in the assay described below at compound concentrations below 4 nM, more preferably at concentrations below 10 μM and most preferably at concentrations less than or equal to 100 μM .

DETERMINATION OF ANTAGONIST ACTIVITY

Test compounds are dissolved in DMSO, diluted in 20 μl KRH buffer so that the final concentration of test compounds in the assay well is between 1 μM and 5 μM , and added to cells prepared as described above. The 96 well plates containing prepared cells and test compounds are incubated in the dark, at room temperature for 0.5 to 6 hours. It is important that the incubation not continue beyond 6 hours. Just prior to determining the fluorescence response, 100 μl capsaicin in KRH buffer at twice the EC_{50} concentration determined as described above is automatically added by the FLIPR instrument to each well of the 96 well plate for a final sample volume of 200 μl and a final capsaicin concentration equal to the EC_{50} . The final concentration of test compounds in the assay wells is between 1 μM and 5 μM . Antagonists of the capsaicin receptor decrease this response by at least about 20%, preferably by at least about 50%, and most preferably by at least 80%, as compared to matched control (*i.e.*, cells treated with capsaicin at twice the EC_{50} concentration in the absence of test compound), at a concentration of 10 micromolar or less, preferably 1 micromolar or less. The concentration of antagonist required to provide a 50% decrease, relative to the response observed in the presence of capsaicin and without antagonist, is the IC_{50} for the antagonist, and is preferably below 1 micromolar, 100 nanomolar, 10 nanomolar or 1 nanomolar.

Certain preferred VR1 modulators are antagonists that are essentially free of agonist activity as demonstrated by the absence of detectable agonist activity in the assay described above at compound concentrations below 4 nM, more preferably at concentrations below 10 μM and most preferably at concentrations less than or equal to 100 μM .

EXAMPLE 7

MICROSOMAL *IN VITRO* HALF-LIFE

This Example illustrates the evaluation of compound half-life values ($t_{1/2}$ values) using a representative liver microsomal half-life assay.

5 Pooled human liver microsomes are obtained from XenoTech LLC (Kansas City, KS). Such liver microsomes may also be obtained from In Vitro Technologies (Baltimore, MD) or Tissue Transformation Technologies (Edison, NJ). Six test reactions are prepared, each containing 25 μ l microsomes, 5 μ l of a 100 μ M solution of test compound, and 399 μ l 0.1 M phosphate buffer (19 mL 0.1 M NaH_2PO_4 , 81 mL 0.1 M Na_2HPO_4 , adjusted to pH 7.4
10 with H_3PO_4). A seventh reaction is prepared as a positive control containing 25 μ l microsomes, 399 μ l 0.1 M phosphate buffer, and 5 μ l of a 100 μ M solution of a compound with known metabolic properties (*e.g.*, DIAZEPAM or CLOZAPINE). Reactions are preincubated at 39°C for 10 minutes.

CoFactor Mixture is prepared by diluting 16.2 mg NADP and 45.4 mg Glucose-6-phosphate in 4 mL 100 mM MgCl_2 . Glucose-6-phosphate dehydrogenase solution is prepared
15 by diluting 214.3 μ l glucose-6-phosphate dehydrogenase suspension (Roche Molecular Biochemicals; Indianapolis, IN) into 1285.7 μ l distilled water. 71 μ l Starting Reaction Mixture (3 mL CoFactor Mixture; 1.2 mL Glucose-6-phosphate dehydrogenase solution) is added to 5 of the 6 test reactions and to the positive control. 71 μ l 100 mM MgCl_2 is added
20 to the sixth test reaction, which is used as a negative control. At each time point (0, 1, 3, 5, and 10 minutes), 75 μ l of each reaction mix is pipetted into a well of a 96-well deep-well plate containing 75 μ l ice-cold acetonitrile. Samples are vortexed and centrifuged 10 minutes at 3500 rpm (Sorval T 6000D centrifuge, H1000B rotor). 75 μ l of supernatant from each reaction is transferred to a well of a 96-well plate containing 150 μ l of a 0.5 μ M solution of a
25 compound with a known LCMS profile (internal standard) per well. LCMS analysis of each sample is carried out and the amount of unmetabolized test compound is measured as AUC, compound concentration vs. time is plotted, and the $t_{1/2}$ value of the test compound is extrapolated.

Preferred compounds provided herein exhibit *in vitro* $t_{1/2}$ values of greater than 10
30 minutes and less than 4 hours, preferably between 30 minutes and 1 hour, in human liver microsomes.

EXAMPLE 8

MDCK TOXICITY ASSAY

This Example illustrates the evaluation of compound toxicity using a Madin Darby canine kidney (MDCK) cell cytotoxicity assay.

1 μ L of test compound is added to each well of a clear bottom 96-well plate
5 (PACKARD, Meriden, CT) to give final concentration of compound in the assay of 10 micromolar, 100 micromolar or 200 micromolar. Solvent without test compound is added to control wells.

MDCK cells, ATCC no. CCL-34 (American Type Culture Collection, Manassas, VA), are maintained in sterile conditions following the instructions in the ATCC production
10 information sheet. Confluent MDCK cells are trypsinized, harvested, and diluted to a concentration of 0.1×10^6 cells/ml with warm (37°C) medium (VITACELL Minimum Essential Medium Eagle, ATCC catalog # 30-2003). 100 μ L of diluted cells is added to each well, except for five standard curve control wells that contain 100 μ L of warm medium without cells. The plate is then incubated at 37°C under 95% O₂, 5% CO₂ for 2 hours with
15 constant shaking. After incubation, 50 μ L of mammalian cell lysis solution (from the PACKARD (Meriden, CT) ATP-LITE-M Luminescent ATP detection kit) is added per well, the wells are covered with PACKARD TOPSEAL stickers, and plates are shaken at approximately 700 rpm on a suitable shaker for 2 minutes.

Compounds causing toxicity will decrease ATP production, relative to untreated cells.
20 The ATP-LITE-M Luminescent ATP detection kit is generally used according to the manufacturer's instructions to measure ATP production in treated and untreated MDCK cells. PACKARD ATP LITE-M reagents are allowed to equilibrate to room temperature. Once equilibrated, the lyophilized substrate solution is reconstituted in 5.5 mL of substrate buffer solution (from kit). Lyophilized ATP standard solution is reconstituted in deionized water to
25 give a 10 mM stock. For the five control wells, 10 μ L of serially diluted PACKARD standard is added to each of the standard curve control wells to yield a final concentration in each subsequent well of 200 nM, 100 nM, 50 nM, 25 nM and 12.5 nM. PACKARD substrate solution (50 μ L) is added to all wells, which are then covered, and the plates are shaken at approximately 700 rpm on a suitable shaker for 2 minutes. A white PACKARD sticker is
30 attached to the bottom of each plate and samples are dark adapted by wrapping plates in foil and placing in the dark for 10 minutes. Luminescence is then measured at 22°C using a luminescence counter (e.g., PACKARD TOPCOUNT Microplate Scintillation and Luminescence Counter or TECAN SPECTRAFLUOR PLUS), and ATP levels calculated

from the standard curve. ATP levels in cells treated with test compound(s) are compared to the levels determined for untreated cells. Cells treated with 10 μ M of a preferred test compound exhibit ATP levels that are at least 80%, preferably at least 90%, of the untreated cells. When a 100 μ M concentration of the test compound is used, cells treated with preferred test compounds exhibit ATP levels that are at least 50%, preferably at least 80%, of the ATP levels detected in untreated cells.

EXAMPLE 9

DORSAL ROOT GANGLION CELL ASSAY

10 This Example illustrates a representative dorsal root ganglion cell assay for evaluating VR1 antagonist or agonist activity of a compound.

DRG are dissected from neonatal rats, dissociated and cultured using standard methods (Aguayo and White (1992) *Brain Research* 570:61-67). After 48 hour incubation, cells are washed once and incubated for 30-60 minutes with the calcium sensitive dye Fluo 4 AM (2.5-10 μ g/ml; TefLabs, Austin, TX). Cells are then washed once. Addition of capsaicin to the cells results in a VR1-dependent increase in intracellular calcium levels which is monitored by a change in Fluo-4 fluorescence with a fluorometer. Data are collected for 60-180 seconds to determine the maximum fluorescent signal.

For antagonist assays, various concentrations of compound are added to the cells. Fluorescent signal is then plotted as a function of compound concentration to identify the concentration required to achieve a 50% inhibition of the capsaicin-activated response, or IC_{50} . Antagonists of the capsaicin receptor preferably have an IC_{50} below 1 micromolar, 100 nanomolar, 10 nanomolar or 1 nanomolar.

For agonist assays, various concentrations of compound are added to the cells without the addition of capsaicin. Compounds that are capsaicin receptor agonists result in a VR1-dependent increase in intracellular calcium levels which is monitored by a change in Fluo-4 fluorescence with a fluorometer. The EC_{50} , or concentration required to achieve 50% of the maximum signal for a capsaicin-activated response, is preferably below 1 micromolar, below 100 nanomolar or below 10 nanomolar.

EXAMPLE 10

ANIMAL MODELS FOR DETERMINING PAIN RELIEF

This Example illustrates representative methods for assessing the degree of pain relief provided by a compound.

5 A. Pain Relief Testing

The following methods may be used to assess pain relief.

MECHANICAL ALLODYNIA

Mechanical allodynia (an abnormal response to an innocuous stimulus) is assessed essentially as described by Chaplan *et al.* (1994) *J. Neurosci. Methods* 53:55-63 and Tal and Eliav (1998) *Pain* 64(3):511-518. A series of von Frey filaments of varying rigidity (typically 8-14 filaments in a series) are applied to the plantar surface of the hind paw with just enough force to bend the filament. The filaments are held in this position for no more than three seconds or until a positive allodynic response is displayed by the rat. A positive allodynic response consists of lifting the affected paw followed immediately by licking or shaking of the paw. The order and frequency with which the individual filaments are applied are determined by using Dixon up-down method. Testing is initiated with the middle hair of the series with subsequent filaments being applied in consecutive fashion, ascending or descending, depending on whether a negative or positive response, respectively, is obtained with the initial filament.

Compounds are effective in reversing or preventing mechanical allodynia-like symptoms if rats treated with such compounds require stimulation with a Von Frey filament of higher rigidity strength to provoke a positive allodynic response as compared to control untreated or vehicle treated rats. Alternatively, or in addition, testing of an animal in chronic pain may be done before and after compound administration. In such an assay, an effective compound results in an increase in the rigidity of the filament needed to induce a response after treatment, as compared to the filament that induces a response before treatment or in an animal that is also in chronic pain but is left untreated or is treated with vehicle. Test compounds are administered before or after onset of pain. When a test compound is administered after pain onset, testing is performed 10 minutes to three hours after administration.

MECHANICAL HYPERALGESIA

Mechanical hyperalgesia (an exaggerated response to painful stimulus) is tested essentially as described by Koch et al. (1996) *Analgesia* 2(3):157-164. Rats are placed in individual compartments of a cage with a warmed, perforated metal floor. Hind paw withdrawal duration (*i.e.*, the amount of time for which the animal holds its paw up before placing it back on the floor) is measured after a mild pinprick to the plantar surface of either hind paw.

Compounds produce a reduction in mechanical hyperalgesia if there is a statistically significant decrease in the duration of hindpaw withdrawal. Test compound may be administered before or after onset of pain. For compounds administered after pain onset, testing is performed 10 minutes to three hours after administration.

THERMAL HYPERALGESIA

Thermal hyperalgesia (an exaggerated response to noxious thermal stimulus) is measured essentially as described by Hargreaves *et al.* (1988) *Pain*. 32(1):77-88. Briefly, a constant radiant heat source is applied the animals' plantar surface of either hind paw. The time to withdrawal (*i.e.*, the amount of time that heat is applied before the animal moves its paw), otherwise described as thermal threshold or latency, determines the animal's hind paw sensitivity to heat.

Compounds produce a reduction in thermal hyperalgesia if there is a statistically significant increase in the time to hindpaw withdrawal (*i.e.*, the thermal threshold to response or latency is increased). Test compound may be administered before or after onset of pain. For compounds administered after pain onset, testing is performed 10 minutes to three hours after administration.

B. Pain Models

Pain may be induced using any of the following methods, to allow testing of analgesic efficacy of a compound. In general, compounds provided herein result in a statistically significant reduction in pain as determined by at least one of the previously described testing methods, using male SD rats and at least one of the following models.

ACUTE INFLAMMATORY PAIN MODEL

Acute inflammatory pain is induced using the carrageenan model essentially as described by Field *et al.* (1997) *Br. J. Pharmacol.* 121(8):1513-1522. 100-200 μ l of 1-2% carrageenan solution is injected into the rats' hind paw. Three to four hours following

injection, the animals' sensitivity to thermal and mechanical stimuli is tested using the methods described above. A test compound (0.01 to 50 mg/kg) is administered to the animal, prior to testing, or prior to injection of carrageenan. The compound can be administered orally or through any parenteral route, or topically on the paw. Compounds that
5 relieve pain in this model result in a statistically significant reduction in mechanical allodynia and/or thermal hyperalgesia.

CHRONIC INFLAMMATORY PAIN MODEL

Chronic inflammatory pain is induced using one of the following protocols:

- 10 1. Essentially as described by Bertorelli *et al.* (1999) *Br. J. Pharmacol.* 128(6):1252-1258, and Stein *et al.* (1998) *Pharmacol. Biochem. Behav.* 31(2):455-51, 200 μ l Complete Freund's Adjuvant (0.1 mg heat killed and dried *M. Tuberculosis*) is injected to the rats' hind paw: 100 μ l into the dorsal surface and 100 μ l into the plantar surface.
- 15 2. Essentially as described by Abbadie *et al.* (1994) *J Neurosci.* 14(10):5865-5871 rats are injected with 150 μ l of CFA (1.5 mg) in the tibio-tarsal joint.

Prior to injection with CFA in either protocol, an individual baseline sensitivity to mechanical and thermal stimulation of the animals' hind paws is obtained for each experimental animal.

Following injection of CFA, rats are tested for thermal hyperalgesia, mechanical
20 allodynia and mechanical hyperalgesia as described above. To verify the development of symptoms, rats are tested on days 5, 6, and 7 following CFA injection. On day 7, animals are treated with a test compound, morphine or vehicle. An oral dose of morphine of 1-5 mg/kg is suitable as positive control. Typically, a dose of 0.01-50 mg/kg of test compound is used. Compounds can be administered as a single bolus prior to testing or once or twice or three
25 times daily, for several days prior to testing. Drugs are administered orally or through any parenteral route, or applied topically to the animal.

Results are expressed as Percent Maximum Potential Efficacy (MPE). 0% MPE is defined as analgesic effect of vehicle, 100% MPE is defined as an animal's return to pre-CFA baseline sensitivity. Compounds that relieve pain in this model result in a MPE of at least
30 30%.

CHRONIC NEUROPATHIC PAIN MODEL

Chronic neuropathic pain is induced using the chronic constriction injury (CCI) to the rat's sciatic nerve essentially as described by Bennett and Xie (1988) *Pain* 33:87-107. Rats

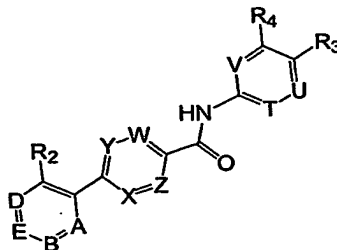
are anesthetized (*e.g.* with an intraperitoneal dose of 50-65 mg/kg pentobarbital with additional doses administered as needed). The lateral aspect of each hind limb is shaved and disinfected. Using aseptic technique, an incision is made on the lateral aspect of the hind limb at the mid thigh level. The biceps femoris is bluntly dissected and the sciatic nerve is exposed. On one hind limb of each animal, four loosely tied ligatures are made around the sciatic nerve approximately 1-2 mm apart. On the other side the sciatic nerve is not ligated and is not manipulated. The muscle is closed with continuous pattern and the skin is closed with wound clips or sutures. Rats are assessed for mechanical allodynia, mechanical hyperalgesia and thermal hyperalgesia as described above.

10 Compounds that relieve pain in this model result in a statistically significant reduction in mechanical allodynia, mechanical hyperalgesia and/or thermal hyperalgesia when administered (0.01-50 mg/kg, orally, parenterally or topically) immediately prior to testing as a single bolus, or for several days: once or twice or three times daily prior to testing.

15 From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

What is claimed is:

1. A compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

A, B, D, E, W, X, Y and Z are independently CR₁ or N;

T, U and V are independently CR₈ or N;

R₁ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L_a-R_a;

R₂ is selected from nitro, cyano, -NHOH, and groups of the formula L_a-R_a; with the proviso that R₂ is not hydrogen;

R₃ and R₄ are:

- (a) each independently selected from (i) hydrogen and halogen; and (ii) C₁-C₈alkyl, C₂-C₈alkyl ether and -(SO₂)C₁-C₆alkyl, each of which is substituted with from 0 to 5 substituents independently chosen from halogen, hydroxy, amino, cyano and nitro; with the proviso that at least one of R₃ and R₄ is not hydrogen; or
- (b) taken together to form a fused ring selected from 5- to 8-membered carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings; and dioxane, wherein each fused ring is substituted with from 0 to 3 substituents independently chosen from halogen, hydroxy, amino, nitro, cyano, C₁-C₆alkyl and C₁-C₆haloalkyl;

R₈ is independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)amino, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂ and -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl;

L_a is independently chosen at each occurrence from a bond, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, S(O)_m, N(R_x), N(R_x)C(=O), N(R_x)S(O)_m, S(O)_mN(R_x) and N[S(O)_mR_x]S(O)_m; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C₁-C₈alkyl; and

R_a is independently selected at each occurrence from:

- (a) hydrogen; and
- (b) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), (5-membered heteroaryl)C₀-C₄alkyl and (5- to 7-membered heterocycloalkyl)C₀-C₄alkyl, each of which is substituted with from 0 to 5 substituents independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, aminocarbonyl, aminoC₁-C₆alkyl, and mono- and di-(C₁-C₆alkyl)amino.
2. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein A is N.
3. A compound or pharmaceutically acceptable form thereof according to claim 1 or claim 2, wherein R₂ is selected from cyano, nitro, NHOH, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄hydroxyalkyl, C₁-C₄alkoxy, C₁-C₄alkylthio, C₁-C₄alkanoyl, aminoC₀-C₄alkyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), (C₅-C₆cycloalkyl)amino, (5- or 6-membered heterocycloalkyl)C₀-C₄alkyl, -N(R_x)SO₂C₁-C₄alkyl and -N(SO₂C₁-C₄alkyl)₂.
4. A compound or pharmaceutically acceptable form thereof according to claim 3, wherein R₂ is cyano, CHO, amino, nitro, methyl, ethyl, propyl, hydroxymethyl, trifluoromethyl, methoxy, ethoxy, propoxy, methylthio, ethylthio, (C₁-C₄alkyl)amino, (C₁-C₄alkyl)aminomethyl, cyclopentylamino, oxadiazolyl, -N(H)SO₂C₁-C₄alkyl, -N(CH₃)SO₂C₁-C₄alkyl or -N(SO₂CH₃)₂.
5. A compound or pharmaceutically acceptable form thereof according to claim 4, wherein R₂ is cyano, CHO, amino, nitro, methyl, trifluoromethyl, methoxy, ethoxy, propoxy, (C₁-C₄alkyl)amino, cyclopentylamino, -N(H)SO₂C₁-C₄alkyl, -N(CH₃)SO₂CH₃ or -N(SO₂CH₃)₂.
6. A compound or pharmaceutically acceptable form thereof according to any one of claims 1-5, wherein B and D are CR₁, and wherein each R₁ at B and D is independently selected from hydrogen, halogen, cyano, C₁-C₄alkyl, C₁-C₄haloalkyl and C₁-C₄alkoxy.
7. A compound or pharmaceutically acceptable form thereof according to any one of claims 1-6, wherein E is N or CR₁, wherein R₁ at E is hydrogen, C₁-C₄alkyl or C₁-C₂alkoxy.
8. A compound or pharmaceutically acceptable form thereof according to any one of claims 1-7, wherein W, Y and Z are CR₁, and wherein each R₁ at W, Y and Z is independently chosen from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-

C₄haloalkyl, C₁-C₄alkoxy, -N(H)SO₂C₁-C₄alkyl, -N(C₁-C₄alkyl)SO₂C₁-C₄alkyl and -N(SO₂C₁-C₄alkyl)₂.

9. A compound or pharmaceutically acceptable form thereof according to claim 8, wherein X is N.

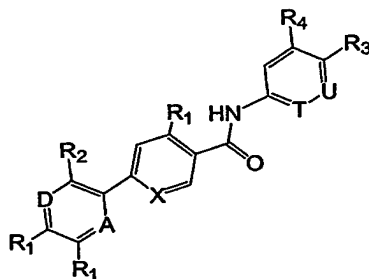
10. A compound or pharmaceutically acceptable form thereof according to claim 8, wherein each R₁ at W, Y and Z is independently chosen from hydrogen, halogen, hydroxy, amino, nitro and C₁-C₄alkyl.

11. A compound or pharmaceutically acceptable form thereof according to claim 8, wherein each R₁ at W, Y and Z is hydrogen.

12. A compound or pharmaceutically acceptable form thereof according to claim 10, wherein X is N or CH.

13. A compound or pharmaceutically acceptable form thereof according to any one of claims 1-12, wherein R₃ and R₄ are independently selected from hydrogen, halogen, C₁-C₄alkyl, C₂-C₄alkyl ether, C₁-C₄haloalkyl, C₁-C₄hydroxyalkyl and -SO₂CF₃; or wherein R₃ and R₄ are taken together to form a fused ring chosen from 5-membered carbocyclic and heterocyclic rings, phenyl, dioxane and dioxepane.

14. A compound or pharmaceutically acceptable form thereof according to claim 1, having the formula:



15. A compound or pharmaceutically acceptable form thereof according to claim 14, wherein:

A, T, U and X are independently N or CH;

D is CH;

each R₁ is independently chosen from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, -N(H)SO₂C₁-C₄alkyl, -N(C₁-C₄alkyl)SO₂C₁-C₄alkyl and -N(SO₂C₁-C₄alkyl)₂;

R₂ is cyano, CHO, amino, nitro, methyl, ethyl, propyl, trifluoromethyl, methoxy, ethoxy, propoxy, methylthio, ethylthio, -N(H)SO₂C₁-C₄alkyl, -N(CH₃)SO₂C₁-C₄alkyl or -N(SO₂CH₃)₂; and

R₃ and R₄ are independently selected from hydrogen, halogen, C₁-C₄alkyl, C₂-C₄alkyl ether, C₁-C₄haloalkyl, C₁-C₄hydroxyalkyl and -SO₂CF₃; or R₃ and R₄ are taken together to form a fused ring chosen from 5-membered carbocyclic and heterocyclic rings, phenyl, dioxane and dioxepane.

16. A compound or pharmaceutically acceptable form thereof according to claim 1, wherein the compound is:

- 2-Amino-N-(4-*tert*-butyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
- 2-Amino-N-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
- 2-Amino-N-(6-trifluoromethyl-pyridin-3-yl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
- 2-Hydroxy-N-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
- 2-Methanesulfonylamino-N-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
- 2-Nitro-N-(4-trifluoromethanesulfonyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
- 2-Nitro-N-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
- 3-Hydroxy-2'-trifluoromethyl-biphenyl-4-carboxylic acid (4-*tert*-butyl-phenyl)-amide;
- 4-(3-Amino-pyridin-2-yl)-N-(4-*tert*-butyl-phenyl)-benzamide;
- 4-(3-Amino-pyridin-4-yl)-N-(4-*tert*-butyl-phenyl)-benzamide;
- 4-(3-Nitro-pyridin-2-yl)-N-(4-trifluoromethyl-phenyl)-benzamide;
- 4-[3-(Butane-1-sulfonylamino)-pyridin-2-yl]-N-(4-*tert*-butyl-phenyl)-benzamide;
- 6-(2,4-Dimethoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide;
- 6-(2,4-Dimethoxy-phenyl)-N-(4-propyl-phenyl)-nicotinamide;
- 6-(2,4-Dimethoxy-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide;
- 6-(2,5-Dimethoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide;
- 6-(2,5-Dimethoxy-phenyl)-N-(4-propyl-phenyl)-nicotinamide;
- 6-(2,5-Dimethyl-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide;
- 6-(2,5-Dimethyl-phenyl)-N-(4-ethyl-phenyl)-nicotinamide;
- 6-(2,5-Dimethyl-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide;

6-(2,5-Dimethyl-phenyl)-N-(4-propyl-phenyl)-nicotinamide;
6-(2,5-Dimethyl-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide;
6-(2,5-Dimethyl-phenyl)-N-indan-5-yl-nicotinamide;
6-(2,6-Dimethoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide;
6-(2,6-Dimethoxy-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide;
6-(2-Acetyl-phenyl)-N-(4-*tert*-butyl-phenyl)-nicotinamide;
6-(2-Amino-phenyl)-N-(4-*tert*-butyl-phenyl)-nicotinamide;
6-(2-Methoxy-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide;
6-(2-Methoxy-phenyl)-N-(4-propyl-phenyl)-nicotinamide;
6-(2-Methoxy-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide;
6-(2-Methylsulfanyl-phenyl)-N-(4-propyl-phenyl)-nicotinamide;
6-(2-Methylsulfanyl-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(3,4-dimethyl-phenyl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(4-chloro-phenyl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(4-ethyl-phenyl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(4-propyl-phenyl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-indan-5-yl-nicotinamide;
6-(5-Fluoro-2-methoxy-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide;
6-(5-Fluoro-2-methoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide;
6-(5-Fluoro-2-methoxy-phenyl)-N-(4-propyl-phenyl)-nicotinamide;
6-(5-Fluoro-2-methoxy-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide;
6-(5-Fluoro-2-methoxy-phenyl)-N-indan-5-yl-nicotinamide;
6-(5-Isopropyl-2-methoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide;
6-Methyl-3'-trifluoromethyl-[2,2']bipyridinyl-5-carboxylic acid (4-trifluoromethyl-phenyl)-
amide;
6-o-Tolyl-N-(2,3,4-trifluoro-phenyl)-nicotinamide;
6-o-Tolyl-N-(3-trifluoromethyl-phenyl)-nicotinamide;
6-o-Tolyl-N-(4-trifluoromethyl-phenyl)-nicotinamide;
6-o-Tolyl-N-p-tolyl-nicotinamide;

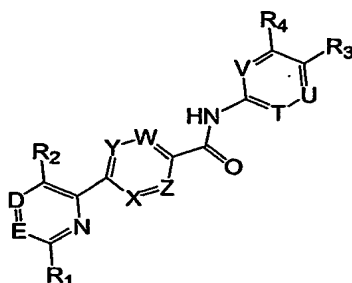
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(2,5-dimethoxy-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(2,5-dimethyl-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(2-methoxy-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-o-tolyl-nicotinamide;
N-(3,4-Dichloro-phenyl)-6-(2-methoxy-phenyl)-nicotinamide;
N-(3,4-Dichloro-phenyl)-6-o-tolyl-nicotinamide;
N-(3,4-Difluoro-phenyl)-6-o-tolyl-nicotinamide;
N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(2,5-dimethyl-phenyl)-nicotinamide;
N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(2-methoxy-phenyl)-nicotinamide;
N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide;
N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(5-isopropyl-2-methoxy-phenyl)-
nicotinamide;
N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-o-tolyl-nicotinamide;
N-(3,4-Dimethyl-phenyl)-6-(2,5-dimethyl-phenyl)-nicotinamide;
N-(3,4-Dimethyl-phenyl)-6-(2-methoxy-phenyl)-nicotinamide;
N-(3,4-Dimethyl-phenyl)-6-(2-methylsulfanyl-phenyl)-nicotinamide;
N-(3,4-Dimethyl-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide;
N-(3,4-Dimethyl-phenyl)-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide;
N-(3,4-Dimethyl-phenyl)-6-o-tolyl-nicotinamide;
N-(3,5-Bis-trifluoromethyl-phenyl)-6-o-tolyl-nicotinamide;
N-(3,5-Dichloro-phenyl)-6-o-tolyl-nicotinamide;
N-(3-Chloro-phenyl)-6-o-tolyl-nicotinamide;
N-(3-Fluoro-4-methyl-phenyl)-6-(2-methoxy-phenyl)-nicotinamide;
N-(3-Fluoro-4-methyl-phenyl)-6-(2-methylsulfanyl-phenyl)-nicotinamide;
N-(3-Fluoro-4-methyl-phenyl)-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide;
N-(3-Fluoro-4-methyl-phenyl)-6-o-tolyl-nicotinamide;
N-(3-Fluoro-phenyl)-6-o-tolyl-nicotinamide;
N-(3-*tert*-Butyl-phenyl)-6-(2,5-dimethyl-phenyl)-nicotinamide;
N-(3-*tert*-Butyl-phenyl)-6-(2-methoxy-phenyl)-nicotinamide;
N-(3-*tert*-Butyl-phenyl)-6-(2-methylsulfanyl-phenyl)-nicotinamide;
N-(3-*tert*-Butyl-phenyl)-6-(5-chloro-2-methoxy-phenyl)-nicotinamide;
N-(3-*tert*-Butyl-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide;

N-(4-Bromo-2-fluoro-phenyl)-6-o-tolyl-nicotinamide;
N-(4-Bromo-3-chloro-phenyl)-6-(2,4-dimethoxy-phenyl)-nicotinamide;
N-(4-Bromo-3-chloro-phenyl)-6-(2,5-dimethoxy-phenyl)-nicotinamide;
N-(4-Bromo-3-chloro-phenyl)-6-(2,5-dimethyl-phenyl)-nicotinamide;
N-(4-Bromo-3-chloro-phenyl)-6-(2,6-dimethoxy-phenyl)-nicotinamide;
N-(4-Bromo-3-chloro-phenyl)-6-(2-methoxy-phenyl)-nicotinamide;
N-(4-Bromo-3-chloro-phenyl)-6-(2-methylsulfanyl-phenyl)-nicotinamide;
N-(4-Bromo-3-chloro-phenyl)-6-(5-chloro-2-methoxy-phenyl)-nicotinamide;
N-(4-Bromo-3-chloro-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide;
N-(4-Bromo-3-chloro-phenyl)-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide;
N-(4-Bromo-3-chloro-phenyl)-6-o-tolyl-nicotinamide;
N-(4-Bromo-3-trifluoromethyl-phenyl)-6-(2-methoxy-phenyl)-nicotinamide;
N-(4-Butyl-phenyl)-6-(2,4-dimethoxy-phenyl)-nicotinamide;
N-(4-Butyl-phenyl)-6-(2,5-dimethyl-phenyl)-nicotinamide;
N-(4-Butyl-phenyl)-6-(2,6-dimethoxy-phenyl)-nicotinamide;
N-(4-Butyl-phenyl)-6-(2-methoxy-phenyl)-nicotinamide;
N-(4-Butyl-phenyl)-6-(2-methylsulfanyl-phenyl)-nicotinamide;
N-(4-Butyl-phenyl)-6-(5-chloro-2-methoxy-phenyl)-nicotinamide;
N-(4-Butyl-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide;
N-(4-Butyl-phenyl)-6-o-tolyl-nicotinamide;
N-(4-Chloro-phenyl)-6-(2,4-dimethoxy-phenyl)-nicotinamide;
N-(4-Chloro-phenyl)-6-(2,5-dimethyl-phenyl)-nicotinamide;
N-(4-Chloro-phenyl)-6-(2-methoxy-phenyl)-nicotinamide;
N-(4-Chloro-phenyl)-6-(2-methylsulfanyl-phenyl)-nicotinamide;
N-(4-Chloro-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide;
N-(4-Chloro-phenyl)-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide;
N-(4-Chloro-phenyl)-6-o-tolyl-nicotinamide;
N-(4-Ethyl-phenyl)-6-(2-methoxy-phenyl)-nicotinamide;
N-(4-Ethyl-phenyl)-6-(2-methylsulfanyl-phenyl)-nicotinamide;
N-(4-Ethyl-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide;
N-(4-Ethyl-phenyl)-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide;
N-(4-Ethyl-phenyl)-6-o-tolyl-nicotinamide;
N-(4-Fluoro-phenyl)-6-o-tolyl-nicotinamide;
N-(4-Isopropyl-phenyl)-6-(2-methoxy-phenyl)-nicotinamide;

N-(4-Isopropyl-phenyl)-6-(2-methylsulfanyl-phenyl)-nicotinamide;
N-(4-Isopropyl-phenyl)-6-o-tolyl-nicotinamide;
N-(4-Propyl-phenyl)-6-o-tolyl-nicotinamide;
N-(4-*tert*-Butyl-2-chloro-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide;
N-(4-*tert*-Butyl-phenyl)-2-hydroxy-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-2-nitro-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-[1,3,4]oxadiazol-2-yl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-cyano-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-cyclopentylamino-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-dimethylaminomethyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-ethanesulfonylamino-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-formyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-hydroxyamino-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-hydroxymethyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-methanesulfonylamino-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-methyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-nitro-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-nitro-pyridin-4-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-propoxy-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-propylamino-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-pyrrolidin-1-ylmethyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-[3-(5-methyl-[1,3,4]oxadiazol-2-yl)-pyridin-2-yl]-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-[3-(methanesulfonyl-methyl-amino)-pyridin-2-yl]-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-[3-(N,N-dimethanesulfonyl)amino-pyridin-2-yl]-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-[3-(N,N-dimethanesulfonyl)amino-pyridin-4-yl]-benzamide;
N-(4-*tert*-Butyl-phenyl)-6-(2,6-dimethyl-phenyl)-nicotinamide;
N-(4-*tert*-Butyl-phenyl)-6-(2-hydroxymethyl-phenyl)-nicotinamide;
N-(4-*tert*-Butyl-phenyl)-6-(2-methanesulfonylamino-phenyl)-nicotinamide;
N-(4-*tert*-Butyl-phenyl)-6-(2-nitro-phenyl)-nicotinamide;
N-(4-*tert*-Butyl-phenyl)-6-(2-trifluoromethyl-phenyl)-nicotinamide;
N-(4-*tert*-Butyl-phenyl)-6-[2-(N,N-dimethanesulfonyl)amino-phenyl]-nicotinamide;
N-(4-*tert*-Butyl-phenyl)-6-o-tolyl-nicotinamide;
N-(4-Trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;

N-(4-Trifluoromethyl-phenyl)-4-[3-(N,N-dimethanesulfonyl)amino-pyridin-2-yl]-benzamide;
 N-(5-Trifluoromethyl-pyridin-2-yl)-4-[3-(N,N-dimethanesulfonyl)amino-pyridin-2-yl]-
 benzamide;
 N-Indan-5-yl-6-(2-methoxy-phenyl)-nicotinamide;
 N-Indan-5-yl-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide; or
 N-Indan-5-yl-6-o-tolyl-nicotinamide.

17. A compound of the formula:



wherein:

D, G, W, X, Y and Z are independently CR₁ or N;

T, U and V are independently CR₈ or N;

R₁ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M;

R₂ is halogen, cyano, nitro or a group of the formula L-M; with the proviso that R₂ is not hydrogen;

R₃ and R₄ are:

(a) independently chosen from R₈; or

(b) taken together to form a fused ring selected from 5- to 8-membered carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings and dioxane, each of which fused ring is substituted with from 0 to 3 substituents independently selected from halogen, hydroxy, amino, nitro, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)amino, C₀-C₄alkyl, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂ and -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl;

R₈ is independently chosen at each occurrence from:

(a) hydrogen, halogen, hydroxy, amino, cyano and nitro; and

(b) C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, -SO₂CF₃, 5- to 7-membered heterocycloalkyl, mono- and di-(C₁-C₆alkyl)amino, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂ and -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl; each of

which is substituted with from 0 to 3 substituents independently selected from hydroxy, halogen, cyano, oxo, C₁-C₄alkyl and C₁-C₄haloalkyl;

L is independently chosen at each occurrence from a bond, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, S(O)_m, N(R_x), C(=O)N(R_x), N(R_x)C(=O), N(R_x)S(O)_m, S(O)_mN(R_x) and N[S(O)_mR_x]S(O)_m; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C₁-C₈alkyl; and

M is independently selected at each occurrence from (a) hydrogen; and (b) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), phenylC₀-C₄alkyl, (5-membered heteroaryl)C₀-C₄alkyl and (5- to 7-membered heterocycloalkyl)C₀-C₄alkyl, each of which is substituted with from 0 to 5 substituents independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, aminocarbonyl, aminoC₁-C₆alkyl and mono- and di-(C₁-C₆alkyl)amino.

18. A compound or pharmaceutically acceptable form thereof according to claim 17, wherein R₃ is selected from:

(a) halogen; and

(b) C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, -SO₂CF₃, C₂-C₆alkyl ether and 5- to 7-membered heterocycloalkyl, each of which is substituted with from 0 to 3 substituents independently selected from hydroxy, halogen, cyano, oxo, C₁-C₄alkyl and C₁-C₄haloalkyl.

19. A compound or pharmaceutically acceptable form thereof according to claim 18, wherein R₃ is C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl or C₁-C₆cyanoalkyl.

20. A compound or pharmaceutically acceptable form thereof according to any one of claims 17-19, wherein W, Y and Z are CR₁, and wherein each R₁ at W, Y and Z is independently selected from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, -N(H)SO₂C₁-C₄alkyl, -N(C₁-C₄alkyl)SO₂C₁-C₄alkyl and -N(SO₂C₁-C₄alkyl)₂.

21. A compound or pharmaceutically acceptable form thereof according to claim 20, wherein X is N.

22. A compound or pharmaceutically acceptable form thereof according to claim 20, wherein each R₁ at W, Y and Z is independently chosen from hydrogen, halogen, amino, hydroxy, nitro, C₁-C₄alkyl and -NH(SO₂)CH₃.

23. A compound or pharmaceutically acceptable form thereof according to claim 21, wherein each R₁ at W, Y and Z is hydrogen.

24. A compound or pharmaceutically acceptable form thereof according to claim 23, wherein X is N or CH.

25. A compound or pharmaceutically acceptable form thereof according to any one of claims 17-24, wherein R₂ is selected from:

(i) halogen, nitro, cyano and -NOH; and

(ii) C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆alkylthio, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, aminoC₀-C₆alkyl, mono- and di-(C₁-C₆alkyl)aminoC₀-C₆alkyl, oxadiazolyl, pyrazolyl, (5- or 6-membered heterocycloalkyl)C₀-C₆alkyl, -N(H)SO₂C₁-C₆alkyl, -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂ and -N(H)SO₂-(C₀-C₂alkyl)-phenyl; each of which is substituted with from 0 to 4 substituents independently chosen from halogen, hydroxy, cyano, C₁-C₄alkyl and C₁-C₄haloalkyl.

26. A compound or pharmaceutically acceptable form thereof according to claim 25, wherein R₂ is selected from fluoro, chloro, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄hydroxyalkyl, C₁-C₄alkoxy, C₁-C₄alkylthio, C₁-C₄alkanoyl, aminoC₀-C₄alkyl, mono- and di-(C₁-C₄alkyl)aminoC₀-C₄alkyl, (C₅-C₆cycloalkyl)amino, (5- or 6-membered heterocycloalkyl)C₀-C₄alkyl, -N(H)SO₂C₁-C₄alkyl, -N(C₁-C₄alkyl)SO₂C₁-C₄alkyl and -N(SO₂C₁-C₄alkyl)₂.

27. A compound or pharmaceutically acceptable form thereof according to claim 26, wherein R₂ is cyano, CHO, amino, nitro, NHOH, methyl, ethyl, propyl, trifluoromethyl, methoxy, ethoxy, propoxy, methylthio, ethylthio, -N(H)SO₂C₁-C₄alkyl, -N(H)SO₂-phenyl, -N(CH₃)SO₂C₁-C₄alkyl or -N(SO₂CH₃)₂.

28. A compound or pharmaceutically acceptable form thereof according to claim 26, wherein R₂ is chloro, fluoro, cyano, nitro, amino, CHO, methyl, trifluoromethyl, C₁-C₄alkoxy, cyclopentylamino, pyrrolidin-1-ylmethyl, hydroxymethyl, oxadiazolyl, C₁-C₄alkylamino, dimethylaminomethyl, -N(CH₃)SO₂CH₃ or -N(SO₂CH₃)₂.

29. A compound or pharmaceutically acceptable form thereof according to claim 17, wherein the compound is:

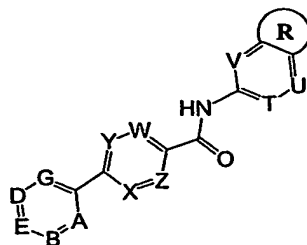
2-Amino-N-(4-*tert*-butyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;

2-Amino-N-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;

2-Amino-N-(6-trifluoromethyl-pyridin-3-yl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
2-Hydroxy-N-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
2-Methanesulfonylamino-N-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
2-Nitro-N-(4-trifluoromethanesulfonyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
2-Nitro-N-(4-trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
2-Nitro-N-(6-trifluoromethyl-pyridin-3-yl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
4-(3-Amino-pyridin-2-yl)-N-(4-*tert*-butyl-phenyl)-benzamide;
4-(3-Benzenesulfonylamino-pyridin-2-yl)-N-(4-*tert*-butyl-phenyl)-benzamide;
4-(3-Chloro-pyridin-2-yl)-N-(4-isopropyl-3-methyl-phenyl)-benzamide;
4-(3-Chloro-pyridin-2-yl)-N-(4-isopropyl-phenyl)-benzamide;
4-(3-Chloro-pyridin-2-yl)-N-(5-trifluoromethyl-pyridin-2-yl)-benzamide;
4-(3-Chloro-pyridin-2-yl)-N-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-benzamide;
4-(3-Chloro-pyridin-2-yl)-N-[4-(2,2,2-trifluoro-1-methyl-ethyl)-phenyl]-benzamide;
4-(3-Chloro-pyridin-2-yl)-N-[4-(2-methoxy-1,1-dimethyl-ethyl)-phenyl]-benzamide;
4-(3-Chloro-pyridin-2-yl)-N-[4-(cyano-dimethyl-methyl)-phenyl]-benzamide;
4-(3-Fluoro-pyridin-2-yl)-N-(4-isopropyl-3-methyl-phenyl)-benzamide;
4-(3-Fluoro-pyridin-2-yl)-N-(4-isopropyl-phenyl)-benzamide;
4-(3-Fluoro-pyridin-2-yl)-N-(4-trifluoromethyl-phenyl)-benzamide;
4-(3-Nitro-pyridin-2-yl)-N-(4-trifluoromethyl-phenyl)-benzamide;
4-[3-(Butane-1-sulfonylamino)-pyridin-2-yl]-N-(4-*tert*-butyl-phenyl)-benzamide;
6-Methyl-3'-trifluoromethyl-[2,2']bipyridinyl-5-carboxylic acid (4-trifluoromethyl-phenyl)-amide;
N-(3,4-Difluoro-phenyl)-4-(3-fluoro-pyridin-2-yl)-benzamide;
N-(4-Butyl-phenyl)-4-(3-chloro-pyridin-2-yl)-benzamide;
N-(4-Cyclopentyl-phenyl)-4-(3-fluoro-pyridin-2-yl)-benzamide;
N-(4-Fluoro-phenyl)-4-(3-fluoro-pyridin-2-yl)-benzamide;
N-(4-*sec*-Butyl-phenyl)-4-(3-fluoro-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-2-hydroxy-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-2-nitro-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3,5-dichloro-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-[1,3,4]oxadiazol-2-yl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-chloro-pyrazin-2-yl)-benzamide;

N-(4-*tert*-Butyl-phenyl)-4-(3-chloro-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-cyano-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-cyclopentylamino-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-dimethylaminomethyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-ethanesulfonylamino-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-fluoro-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-formyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-hydroxyamino-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-hydroxymethyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-methanesulfonylamino-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-methyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-nitro-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-phenylmethanesulfonylamino-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-propoxy-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-propylamino-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-pyrrolidin-1-ylmethyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-[3-(4-fluoro-benzenesulfonylamino)-pyridin-2-yl]-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-[3-(5-methyl-[1,3,4]oxadiazol-2-yl)-pyridin-2-yl]-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-[3-(methanesulfonyl-methyl-amino)-pyridin-2-yl]-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-[3-(N,N-dimethanesulfonyl)amino-pyridin-2-yl]-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-[3-(toluene-4-sulfonylamino)-pyridin-2-yl]-benzamide;
N-(4-Trifluoromethyl-phenyl)-4-(3-trifluoromethyl-pyridin-2-yl)-benzamide;
N-(4-Trifluoromethyl-phenyl)-4-[3-(N,N-dimethanesulfonyl)amino-pyridin-2-yl]-benzamide;
N-(5-Trifluoromethyl-pyridin-2-yl)-4-[3-(N,N-dimethanesulfonyl)amino-pyridin-2-yl]-benzamide; or
N-[4-(3-Ethyl-2,6-dioxo-piperidin-3-yl)-phenyl]-4-(3-fluoro-pyridin-2-yl)-benzamide.

30. A compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

A, B, E, D and G are independently CH, CR₇ or N; with the proviso that at least one of G, D and E is CR₇;

W, X, Y and Z are independently chosen from CR₁ and N;

T, U and V are independently chosen from CR₈ and N;

(R) represents a fused 5- or 7-membered carbocyclic or heterocyclic ring or a fused dioxane ring, wherein the fused ring is substituted with from 0 to 3 substituents independently selected from oxo, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy and C₁-C₄haloalkoxy;

R₁ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M;

R₇ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M; with the proviso that R₇ is not hydrogen;

R₈ is independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)amino, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂ and -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl;

L is independently chosen at each occurrence from a bond, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, S(O)_m, N(R_x), C(=O)N(R_x), N(R_x)C(=O), N(R_x)S(O)_m, S(O)_mN(R_x) and N[S(O)_mR_x]S(O)_m; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C₁-C₈alkyl; and

M is independently selected at each occurrence from:

(a) hydrogen, and

(b) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), phenylC₀-C₄alkyl, (5-membered heteroaryl)C₀-C₄alkyl and (5- to 7-membered heterocycloalkyl)C₀-C₄alkyl, each of which is substituted with from 0 to 5 substituents

independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, aminocarbonyl, aminoC₁-C₆alkyl and mono- and di-(C₁-C₆alkyl)amino.

31. A compound or pharmaceutically acceptable form thereof according to claim 30, wherein at least two of W, X, Y and Z are CR₁, and at least one of T and U is CR₈.

32. A compound or pharmaceutically acceptable form thereof according to claim 30, wherein W, Y and Z are CR₁, and wherein each R₁ is independently chosen from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, -N(H)SO₂C₁-C₄alkyl, -N(C₁-C₄alkyl)SO₂C₁-C₄alkyl and -N(SO₂C₁-C₄alkyl)₂.

33. A compound or pharmaceutically acceptable form thereof according to claim 32, wherein each R₁ is independently chosen from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl and C₁-C₄alkoxy.

34. A compound or pharmaceutically acceptable form thereof according to claim 33, wherein each R₁ is hydrogen, and wherein X is N or CH.

35. A compound or pharmaceutically acceptable form thereof according to any one of claims 30-34, wherein X is N.

36. A compound or pharmaceutically acceptable form thereof according to any one of claims 30-35, wherein $\textcircled{\text{R}}$ is selected from cyclopentene, thiazole, dioxolane, dioxane and dioxepane, each of which is substituted with from 0 to 2 substituents independently selected from oxo, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, and C₁-C₄haloalkoxy.

37. A compound or pharmaceutically acceptable form thereof according to claim 36, wherein $\textcircled{\text{R}}$ is cyclopentene, cyclopentene substituted with oxo, thiazole or methylthiazole.

38. A compound or pharmaceutically acceptable form thereof according to claim 36, wherein $\textcircled{\text{R}}$ is dioxolane, dioxane or dioxepane.

39. A compound or pharmaceutically acceptable form thereof according to any one of claims 30-38, wherein G is CR₇.

40. A compound or pharmaceutically acceptable form thereof according to claim 39, wherein B, D and E are CH or CR₇.

41. A compound or pharmaceutically acceptable form thereof according to claim 39 or claim 40, wherein A is N or CH.

42. A compound or pharmaceutically acceptable form thereof according to claim 39, wherein R₇ at the G position is cyano, chloro, fluoro, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄hydroxyalkyl, C₁-C₄alkoxy, C₁-C₄alkylthio, C₁-C₄alkanoyl, aminoC₀-C₄alkyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), (C₅-C₆cycloalkyl)amino, (5- or 6-membered heterocycloalkyl)C₀-C₄alkyl, -N(H)SO₂C₁-C₄alkyl, -N(H)SO₂-(C₀-C₂alkyl)-phenyl, -N(C₁-C₄alkyl)SO₂C₁-C₄alkyl or -N(SO₂C₁-C₄alkyl)₂.

43. A compound or pharmaceutically acceptable form thereof according to claim 30, wherein each R₇ is independently selected from halogen, amino, cyano, nitro, CHO, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, C₁-C₄alkylthio, -N(H)SO₂C₁-C₄alkyl, -N(CH₃)SO₂C₁-C₄alkyl and -N(SO₂CH₃)₂.

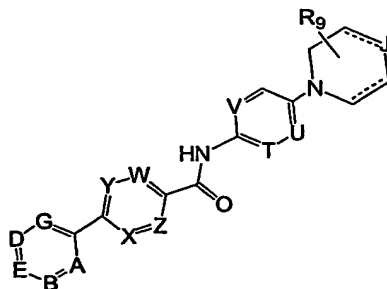
44. A compound or pharmaceutically acceptable form thereof according to claim 30, wherein the compound is:

- 6-(2,4-Difluoro-phenyl)-N-indan-5-yl-nicotinamide;
- 6-(2,5-Dimethyl-phenyl)-N-indan-5-yl-nicotinamide;
- 6-(2-Chloro-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide;
- 6-(2-Fluoro-phenyl)-N-(1-oxo-indan-5-yl)-nicotinamide;
- 6-(2-Fluoro-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide;
- 6-(2-Fluoro-phenyl)-N-indan-5-yl-nicotinamide;
- 6-(2-Methoxy-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide;
- 6-(3,4-Difluoro-phenyl)-N-indan-5-yl-nicotinamide;
- 6-(3,4-Dimethyl-phenyl)-N-indan-5-yl-nicotinamide;
- 6-(3-Chloro-phenyl)-N-indan-5-yl-nicotinamide;
- 6-(3-Ethoxy-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide;
- 6-(3-Ethoxy-phenyl)-N-indan-5-yl-nicotinamide;
- 6-(3-Fluoro-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide;
- 6-(3-Fluoro-phenyl)-N-indan-5-yl-nicotinamide;
- 6-(3-Isopropyl-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide;

6-(3-Methoxy-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide;
6-(4-Butyl-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide;
6-(4-Chloro-phenyl)-N-indan-5-yl-nicotinamide;
6-(4-Fluoro-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide;
6-(4-Fluoro-phenyl)-N-indan-5-yl-nicotinamide;
6-(4-Isopropyl-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-indan-5-yl-nicotinamide;
6-(5-Fluoro-2-methoxy-phenyl)-N-indan-5-yl-nicotinamide;
6-Biphenyl-3-yl-N-indan-5-yl-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(2,5-dimethoxy-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(2,5-dimethyl-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(2-fluoro-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(2-methoxy-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(3-ethoxy-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(3-fluoro-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(3-isopropyl-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(3-methoxy-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(3-trifluoromethoxy-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(4-isopropyl-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-m-tolyl-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-o-tolyl-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-p-tolyl-nicotinamide;
N-(2-Methyl-benzothiazol-5-yl)-6-(3-trifluoromethoxy-phenyl)-nicotinamide;
N-(2-Methyl-benzothiazol-5-yl)-6-m-tolyl-nicotinamide;
N-(2-Methyl-benzothiazol-5-yl)-6-p-tolyl-nicotinamide;
N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(2,5-dimethyl-phenyl)-nicotinamide;
N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(2-fluoro-phenyl)-nicotinamide;
N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(2-methoxy-phenyl)-nicotinamide;
N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(3-fluoro-phenyl)-nicotinamide;
N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(3-isopropyl-phenyl)-nicotinamide;

N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(3-methoxy-phenyl)-nicotinamide;
 N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(3-trifluoromethoxy-phenyl)-nicotinamide;
 N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(4-fluoro-phenyl)-nicotinamide;
 N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(4-isopropyl-phenyl)-nicotinamide;
 N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide;
 N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(5-isopropyl-2-methoxy-phenyl)-
 nicotinamide;
 N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-m-tolyl-nicotinamide;
 N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-o-tolyl-nicotinamide;
 N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-p-tolyl-nicotinamide;
 N-Indan-5-yl-6-(2-methoxy-phenyl)-nicotinamide;
 N-Indan-5-yl-6-(3,4,5-trimethoxy-phenyl)-nicotinamide;
 N-Indan-5-yl-6-(3-isopropyl-phenyl)-nicotinamide;
 N-Indan-5-yl-6-(3-methoxy-phenyl)-nicotinamide;
 N-Indan-5-yl-6-(3-trifluoromethoxy-phenyl)-nicotinamide;
 N-Indan-5-yl-6-(3-trifluoromethyl-phenyl)-nicotinamide;
 N-Indan-5-yl-6-(4-isopropyl-phenyl)-nicotinamide;
 N-Indan-5-yl-6-(4-methoxy-phenyl)-nicotinamide;
 N-Indan-5-yl-6-(5-isopropyl-2-methoxy-phenyl)-nicotinamide;
 N-Indan-5-yl-6-m-tolyl-nicotinamide;
 N-Indan-5-yl-6-o-tolyl-nicotinamide; or
 N-Indan-5-yl-6-p-tolyl-nicotinamide.

45. A compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

J is N, NH, O or S;

A, B, E, D and G are independently CH, CR₇ or N; with the proviso that at least one of G, D and E is CR₇;

W, X, Y and Z are independently CR₁ or N;

T, U and V are independently CR₈ or N;

R₁ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-R_a;

R₇ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-R_a, with the proviso that R₇ is not hydrogen;

R₈ is independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)amino, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂ and -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl;

R₉ represents from 0 to 2 substituents independently chosen from halogen, cyano, nitro, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₄haloalkyl, C₁-C₄haloalkoxy, mono- and di-(C₁-C₆alkyl)amino, and C₂-C₆alkyl ether;

L is independently chosen at each occurrence from a bond, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, S(O)_m, N(R_x), C(=O)N(R_x), N(R_x)C(=O), N(R_x)S(O)_m, S(O)_mN(R_x) and N[S(O)_mR_x]S(O)_m; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C₁-C₈alkyl; and

R_a is independently selected at each occurrence from:

(a) hydrogen; and

(b) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), and (5- to 7-membered heterocycloalkyl)C₀-C₄alkyl, each of which is substituted with from 0 to 5 substituents independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, aminocarbonyl, aminoC₁-C₆alkyl and mono- and di-(C₁-C₆alkyl)amino.

46. A compound or pharmaceutically acceptable form thereof according to claim 45, wherein at least two of W, X, Y and Z are CR₁, at least one of T and U is CR₈, and each R₁ and R₈ is independently chosen from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl and C₁-C₄alkoxy.

47. A compound or pharmaceutically acceptable form thereof according to claim 46, wherein W, Y and Z are CR₁, and wherein each R₁ is independently chosen from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, -N(H)SO₂C₁-C₄alkyl, -N(C₁-C₄alkyl)SO₂C₁-C₄alkyl and -N(SO₂C₁-C₄alkyl)₂.

48. A compound or pharmaceutically acceptable form thereof according to claim 47, wherein each R₁ is independently chosen from hydrogen, halogen, hydroxy and C₁-C₄alkyl.

49. A compound or pharmaceutically acceptable form thereof according to claim 48, wherein R₁ at W, Y and Z is hydrogen, and wherein X is N or CH.

50. A compound or pharmaceutically acceptable form thereof according to claim 46, wherein X is N.

51. A compound or pharmaceutically acceptable form thereof according to claim 45, wherein A is N or CH.

52. A compound or pharmaceutically acceptable form thereof according to claim 45, wherein G is CR₇.

53. A compound or pharmaceutically acceptable form thereof according to claim 52, wherein R₇ at the G position is cyano, chloro, fluoro, nitro, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄hydroxyalkyl, C₁-C₄alkoxy, C₁-C₄alkylthio, C₁-C₄alkanoyl, aminoC₀-C₄alkyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), (C₅-C₆cycloalkyl)amino, (5- or 6-membered heterocycloalkyl)C₀-C₄alkyl, -N(H)SO₂C₁-C₄alkyl, -N(C₁-C₄alkyl)SO₂C₁-C₄alkyl or -N(SO₂C₁-C₄alkyl)₂.

54. A compound or pharmaceutically acceptable form thereof according to claim 45, wherein each R₇ is independently selected from halogen, amino, cyano, nitro, CHO, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, C₁-C₄alkylthio, -N(H)SO₂C₁-C₄alkyl, -N(CH₃)SO₂C₁-C₄alkyl and -N(SO₂CH₃)₂.

55. A compound or pharmaceutically acceptable form thereof according to claim 45, wherein J is O.

56. A compound or pharmaceutically acceptable form thereof according to claim 45, wherein R₉ represents from 0 to 2 substituents independently chosen from halogen, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₄haloalkyl and C₁-C₄haloalkoxy.

57. A compound or pharmaceutically acceptable form thereof according to claim 45, wherein R₉ represents 0 substituents.

58. A compounds or form thereof according to claim 45, wherein:

J is O;

each R₇ is independently selected from halogen, amino, cyano, nitro, CHO, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, C₁-C₄alkylthio, -N(H)SO₂C₁-C₄alkyl, -N(CH₃)SO₂C₁-C₄alkyl and -N(SO₂CH₃)₂;

R₁ at W, Y and Z is CR₁, wherein each R₁ is independently chosen from hydrogen, halogen, hydroxy and C₁-C₄alkyl;

A is N or CH; and

T and U are independently N or CH.

59. A compound or pharmaceutically acceptable form thereof according to claim 45, wherein the compound is:

6-(2,5-Dimethyl-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide;

6-(2-Chloro-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide;

6-(2-Fluoro-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide;

6-(2-Methoxy-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide;

6-(3,4-Dimethyl-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide;

6-(3,5-Dimethyl-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide;

6-(3-Isopropyl-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide;

6-(4-Isopropyl-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide;

6-(5-Isopropyl-2-methoxy-phenyl)-N-(4-morpholin-4-yl-phenyl)-nicotinamide;

N-(3-Chloro-4-morpholin-4-yl-phenyl)-6-(2-chloro-phenyl)-nicotinamide;

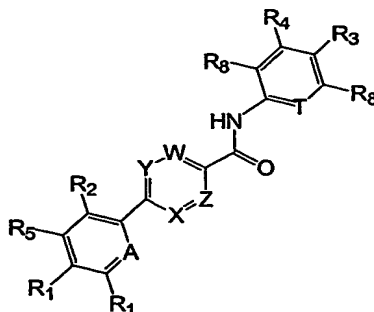
N-(3-Chloro-4-morpholin-4-yl-phenyl)-6-(2-fluoro-phenyl)-nicotinamide;

N-(3-Chloro-4-morpholin-4-yl-phenyl)-6-o-tolyl-nicotinamide;

N-(4-Morpholin-4-yl-phenyl)-6-m-tolyl-nicotinamide; or

N-(4-Morpholin-4-yl-phenyl)-6-o-tolyl-nicotinamide.

60. A compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

A, T, W, X, Y, Z are independently CR₁ or N;

each R₁ and R₈ is independently chosen from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₄haloalkyl and C₁-C₄haloalkoxy;

either:

- (a) R₂ is a halogen and R₅ is hydrogen; or
- (b) R₂ is hydrogen and R₅ is a halogen; and

with regard to R₃ and R₄:

- (a) R₃ is C₁-C₆alkyl and R₄ is hydrogen, halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₄haloalkyl or C₁-C₄haloalkoxy;
- (b) R₃ is hydrogen, halogen, amino, cyano or C₁-C₄alkoxy; and R₄ is halogen, hydroxy, amino, cyano, C₁-C₄alkyl or C₁-C₄alkoxy; or
- (c) R₃ and R₄ are taken together to form a 5- or 6-membered partially saturated carbocycle substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, cyano, nitro, oxo, C₁-C₄alkyl and C₁-C₄alkoxy.

61. A compound or pharmaceutically acceptable form thereof according to claim 60, wherein:

W and X are CH;

A and T are independently CH or N;

Each R₈ is hydrogen; and

each R₁ is hydrogen or halogen.

62. A compound of form thereof according to claim 61, wherein R₃ is C₁-C₆alkyl and R₄ is hydrogen, methyl or halogen.

63. A compound or pharmaceutically acceptable form thereof according to claim 61, wherein R₃ is hydrogen or halogen and R₄ is halogen.

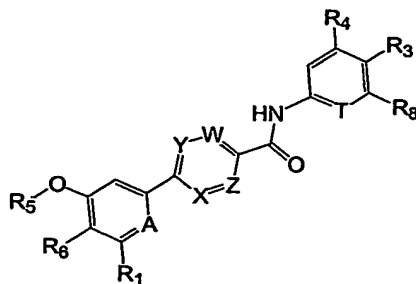
64. A compound or pharmaceutically acceptable form thereof according to claim 60, wherein the compound is:

2'-Chloro-biphenyl-4-carboxylic acid (4-*tert*-butyl-phenyl)-amide;
4-(3-Chloro-pyridin-2-yl)-N-(4-isopropyl-3-methyl-phenyl)-benzamide;
4-(3-Chloro-pyridin-2-yl)-N-(4-isopropyl-phenyl)-benzamide;
4-(3-Fluoro-pyridin-2-yl)-N-(4-isopropyl-3-methyl-phenyl)-benzamide;
4-(3-Fluoro-pyridin-2-yl)-N-(4-isopropyl-phenyl)-benzamide;
5-(2-Chloro-phenyl)-pyrazine-2-carboxylic acid (4-*sec*-butyl-phenyl)-amide;
5-(2-Chloro-phenyl)-pyrazine-2-carboxylic acid (4-*tert*-butyl-phenyl)-amide;
5-(2-Chloro-phenyl)-pyridine-2-carboxylic acid (4-*tert*-butyl-phenyl)-amide;
6-(2,4-Difluoro-phenyl)-N-(3,4-dimethyl-phenyl)-nicotinamide;
6-(2,4-Difluoro-phenyl)-N-indan-5-yl-nicotinamide;
6-(2-Chloro-phenyl)-N-(2,3,4-trifluoro-phenyl)-nicotinamide;
6-(2-Chloro-phenyl)-N-(3,4-dichloro-phenyl)-nicotinamide;
6-(2-Chloro-phenyl)-N-(3,4-difluoro-phenyl)-nicotinamide;
6-(2-Chloro-phenyl)-N-(3,5-dichloro-phenyl)-nicotinamide;
6-(2-Chloro-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide;
6-(2-Chloro-phenyl)-N-(3-fluoro-phenyl)-nicotinamide;
6-(2-Chloro-phenyl)-N-(3-methoxy-phenyl)-nicotinamide;
6-(2-Chloro-phenyl)-N-(4-ethyl-phenyl)-nicotinamide;
6-(2-Chloro-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide;
6-(2-Chloro-phenyl)-N-(4-propyl-phenyl)-nicotinamide;
6-(2-Chloro-phenyl)-N-*m*-tolyl-nicotinamide;
6-(2-Fluoro-phenyl)-N-(1-oxo-indan-5-yl)-nicotinamide;
6-(2-Fluoro-phenyl)-N-(3-methoxy-phenyl)-nicotinamide;
6-(2-Fluoro-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide;
6-(2-Fluoro-phenyl)-N-(4-propyl-phenyl)-nicotinamide;
6-(2-Fluoro-phenyl)-N-indan-5-yl-nicotinamide;
6-(2-Fluoro-phenyl)-N-*m*-tolyl-nicotinamide;
6-(3,4-Difluoro-phenyl)-N-(3,4-dimethyl-phenyl)-nicotinamide;
6-(3,4-Difluoro-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide;

6-(3,4-Difluoro-phenyl)-N-indan-5-yl-nicotinamide;
6-(3-Chloro-phenyl)-N-(3,4-dimethyl-phenyl)-nicotinamide;
6-(3-Chloro-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide;
6-(3-Chloro-phenyl)-N-(4-ethyl-phenyl)-nicotinamide;
6-(3-Chloro-phenyl)-N-indan-5-yl-nicotinamide;
6-(3-Fluoro-phenyl)-N-(3-methoxy-phenyl)-nicotinamide;
6-(3-Fluoro-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide;
6-(3-Fluoro-phenyl)-N-(4-propyl-phenyl)-nicotinamide;
6-(3-Fluoro-phenyl)-N-indan-5-yl-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(3,4-dimethyl-phenyl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(3-methoxy-phenyl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(4-ethyl-phenyl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-(4-propyl-phenyl)-nicotinamide;
6-(5-Chloro-2-methoxy-phenyl)-N-indan-5-yl-nicotinamide;
6-(5-Fluoro-2-methoxy-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide;
6-(5-Fluoro-2-methoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide;
6-(5-Fluoro-2-methoxy-phenyl)-N-(4-propyl-phenyl)-nicotinamide;
6-(5-Fluoro-2-methoxy-phenyl)-N-indan-5-yl-nicotinamide;
N-(3,4-Dichloro-phenyl)-6-(2-fluoro-phenyl)-nicotinamide;
N-(3,4-Difluoro-phenyl)-6-(2-fluoro-phenyl)-nicotinamide;
N-(3,4-Dimethoxy-phenyl)-6-(2-fluoro-phenyl)-nicotinamide;
N-(3,4-Dimethyl-phenyl)-6-(2-fluoro-phenyl)-nicotinamide;
N-(3,4-Dimethyl-phenyl)-6-(3-fluoro-phenyl)-nicotinamide;
N-(3,4-Dimethyl-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide;
N-(3,5-Dichloro-phenyl)-6-(2-fluoro-phenyl)-nicotinamide;
N-(3-Chloro-phenyl)-6-(2-chloro-phenyl)-nicotinamide;
N-(3-Chloro-phenyl)-6-(2-fluoro-phenyl)-nicotinamide;
N-(3-Fluoro-4-methyl-phenyl)-6-(2-fluoro-phenyl)-nicotinamide;
N-(3-Fluoro-4-methyl-phenyl)-6-(3-fluoro-phenyl)-nicotinamide;
N-(3-Fluoro-phenyl)-6-(2-fluoro-phenyl)-nicotinamide;
N-(3-*tert*-Butyl-phenyl)-6-(2,4-difluoro-phenyl)-nicotinamide;
N-(3-*tert*-Butyl-phenyl)-6-(2-chloro-phenyl)-nicotinamide;

N-(3-*tert*-Butyl-phenyl)-6-(2-fluoro-phenyl)-nicotinamide;
N-(3-*tert*-Butyl-phenyl)-6-(3,4-difluoro-phenyl)-nicotinamide;
N-(3-*tert*-Butyl-phenyl)-6-(3-chloro-phenyl)-nicotinamide;
N-(3-*tert*-Butyl-phenyl)-6-(3-fluoro-phenyl)-nicotinamide;
N-(3-*tert*-Butyl-phenyl)-6-(5-chloro-2-methoxy-phenyl)-nicotinamide;
N-(3-*tert*-Butyl-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide;
N-(4-Bromo-3-chloro-phenyl)-6-(2-chloro-phenyl)-nicotinamide;
N-(4-Bromo-3-chloro-phenyl)-6-(2-fluoro-phenyl)-nicotinamide;
N-(4-Bromo-3-chloro-phenyl)-6-(3-fluoro-phenyl)-nicotinamide;
N-(4-Butyl-phenyl)-4-(3-chloro-pyridin-2-yl)-benzamide;
N-(4-Butyl-phenyl)-6-(2-chloro-phenyl)-nicotinamide;
N-(4-Butyl-phenyl)-6-(2-fluoro-phenyl)-nicotinamide;
N-(4-Butyl-phenyl)-6-(5-chloro-2-methoxy-phenyl)-nicotinamide;
N-(4-Butyl-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide;
N-(4-Ethyl-phenyl)-6-(2-fluoro-phenyl)-nicotinamide;
N-(4-Ethyl-phenyl)-6-(3-fluoro-phenyl)-nicotinamide;
N-(4-Ethyl-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide;
N-(4-*sec*-Butyl-phenyl)-4-(3-fluoro-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-2-chloro-phenyl)-6-(5-fluoro-2-methoxy-phenyl)-nicotinamide;
N-(4-*tert*-Butyl-phenyl)-4-(3,5-dichloro-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-chloro-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-4-(3-fluoro-pyridin-2-yl)-benzamide;
N-(4-*tert*-Butyl-phenyl)-5-chloro-6-(2-chloro-phenyl)-nicotinamide;
N-(4-*tert*-Butyl-phenyl)-6-(2,4-difluoro-phenyl)-nicotinamide;
N-(4-*tert*-Butyl-phenyl)-6-(2,6-difluoro-phenyl)-nicotinamide;
N-(4-*tert*-Butyl-phenyl)-6-(2-chloro-4-ethoxy-phenyl)-nicotinamide;
N-(4-*tert*-Butyl-phenyl)-6-(2-chloro-phenyl)-4-hydroxy-nicotinamide;
N-(4-*tert*-Butyl-phenyl)-6-(2-chloro-phenyl)-nicotinamide;
N-(4-*tert*-Butyl-phenyl)-6-(2-fluoro-phenyl)-nicotinamide; or
N-(4-*tert*-Butyl-phenyl)-6-(3-fluoro-phenyl)-nicotinamide.

65. A compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

A and T are independently CH or N;

W, X, Y and Z are independently CR₁ or N;

R₁ and R₈ are independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₄haloalkyl and C₁-C₄haloalkoxy;

R₃ and R₄ are:

- (a) independently chosen from hydrogen, halogen, hydroxy, amino, cyano, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₄haloalkyl and C₁-C₄haloalkoxy; or
- (b) taken together to form a fused ring chosen from 5- to 7-membered partially saturated carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings and dioxane, wherein the fused ring is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, amino, cyano, nitro, oxo, C₁-C₄alkyl, and C₁-C₄alkoxy;

R₅ is:

- (a) C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkenyl or C₁-C₆alkynyl; or
 - (b) taken together with R₆ to form a fused 5- to 7-membered partially saturated heterocycle;
- and

R₆ is:

- (a) hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₄haloalkyl or C₁-C₄haloalkoxy; or
- (b) taken together with R₅ to form a fused 5- to 7-membered partially saturated heterocycle.

66. A compound or pharmaceutically acceptable form thereof according to claim 65, wherein R₃ and R₄ are taken together to form a fused cyclopentene, thiazole, dioxolane or dioxane ring, each of which is unsubstituted or substituted with a methyl group.

67. A compound or pharmaceutically acceptable form thereof according to claim 65, wherein R₃ is C₁-C₆alkyl or halogen and R₄ is hydrogen, C₁-C₆alkyl or halogen.

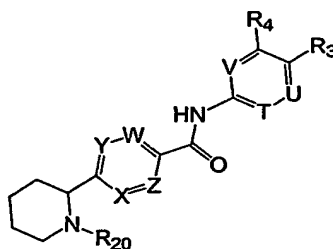
68. A compound or pharmaceutically acceptable form thereof according to claim 65, wherein each R₁ and R₈ is hydrogen.

69. A compound or pharmaceutically acceptable form thereof according to claim 65, wherein the compound is:

6-(3,4-Dimethoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide;
6-(3-Ethoxy-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide;
6-(3-Ethoxy-phenyl)-N-(3-fluoro-4-methyl-phenyl)-nicotinamide;
6-(3-Ethoxy-phenyl)-N-(3-methoxy-phenyl)-nicotinamide;
6-(3-Ethoxy-phenyl)-N-(4-isopropyl-phenyl)-nicotinamide;
6-(3-Ethoxy-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide;
6-(3-Ethoxy-phenyl)-N-indan-5-yl-nicotinamide;
6-(3-Methoxy-phenyl)-N-(2-methyl-benzothiazol-5-yl)-nicotinamide;
6-(3-Methoxy-phenyl)-N-(4-propyl-phenyl)-nicotinamide;
6-(3-Trifluoromethoxy-phenyl)-N-(4-trifluoromethyl-phenyl)-nicotinamide;
6-Benzo[1,3]dioxol-5-yl-N-(2-methyl-benzothiazol-5-yl)-nicotinamide;
6-Benzo[1,3]dioxol-5-yl-N-(3,4-dimethyl-phenyl)-nicotinamide;
6-Benzo[1,3]dioxol-5-yl-N-(3-methoxy-phenyl)-nicotinamide;
6-Benzo[1,3]dioxol-5-yl-N-(3-*tert*-butyl-phenyl)-nicotinamide;
6-Benzo[1,3]dioxol-5-yl-N-(4-isopropyl-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(3-ethoxy-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(3-methoxy-phenyl)-nicotinamide;
N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-6-(3-trifluoromethoxy-phenyl)-nicotinamide;
N-(2-Methyl-benzothiazol-5-yl)-6-(3-trifluoromethoxy-phenyl)-nicotinamide;
N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(3-methoxy-phenyl)-nicotinamide;
N-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-6-(3-trifluoromethoxy-phenyl)-nicotinamide;
N-(3,4-Dimethyl-phenyl)-6-(3-ethoxy-phenyl)-nicotinamide;
N-(3,4-Dimethyl-phenyl)-6-(3-methoxy-phenyl)-nicotinamide;
N-(3,4-Dimethyl-phenyl)-6-(3-trifluoromethoxy-phenyl)-nicotinamide;
N-(3-Fluoro-4-methyl-phenyl)-6-(3-methoxy-phenyl)-nicotinamide;
N-(3-Methoxy-phenyl)-6-(3,4,5-trimethoxy-phenyl)-nicotinamide;

N-(3-Methoxy-phenyl)-6-(3-trifluoromethoxy-phenyl)-nicotinamide;
 N-(3-*tert*-Butyl-phenyl)-6-(3,4,5-trimethoxy-phenyl)-nicotinamide;
 N-(3-*tert*-Butyl-phenyl)-6-(3-methoxy-phenyl)-nicotinamide;
 N-(3-*tert*-Butyl-phenyl)-6-(4-trifluoromethoxy-phenyl)-nicotinamide;
 N-(4-Bromo-3-chloro-phenyl)-6-(3,4,5-trimethoxy-phenyl)-nicotinamide;
 N-(4-Bromo-3-chloro-phenyl)-6-(3,4-dimethoxy-phenyl)-nicotinamide;
 N-(4-Bromo-3-chloro-phenyl)-6-(3-ethoxy-phenyl)-nicotinamide;
 N-(4-Bromo-3-chloro-phenyl)-6-(3-methoxy-phenyl)-nicotinamide;
 N-(4-Butyl-phenyl)-6-(3-methoxy-phenyl)-nicotinamide;
 N-(4-Chloro-phenyl)-6-(3-ethoxy-phenyl)-nicotinamide;
 N-(4-Chloro-phenyl)-6-(3-methoxy-phenyl)-nicotinamide;
 N-(4-Ethyl-phenyl)-6-(3,4,5-trimethoxy-phenyl)-nicotinamide;
 N-(4-Ethyl-phenyl)-6-(3-methoxy-phenyl)-nicotinamide;
 N-(4-Isopropyl-phenyl)-6-(3,4,5-trimethoxy-phenyl)-nicotinamide;
 N-(4-Isopropyl-phenyl)-6-(3-trifluoromethoxy-phenyl)-nicotinamide;
 N-(4-*tert*-Butyl-phenyl)-6-(3-methoxy-phenyl)-nicotinamide;
 N-Indan-5-yl-6-(3,4,5-trimethoxy-phenyl)-nicotinamide;
 N-Indan-5-yl-6-(3-methoxy-phenyl)-nicotinamide; or
 N-Indan-5-yl-6-(3-trifluoromethoxy-phenyl)-nicotinamide.

70. A compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

T, U, V, W, X, Y and Z are independently CR₁ or N;

R₁ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M;

R₃ and R₄ are:

(a) independently chosen from R₁; or

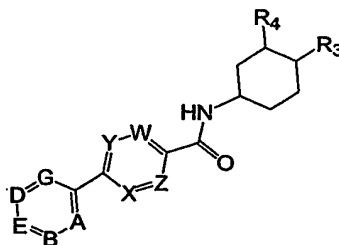
(b) taken together to form a fused ring selected from 5- to 8-membered carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings and dioxane, each of which fused ring is substituted with from 0 to 3 substituents independently selected from halogen, hydroxy, amino, nitro, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)amino, C₀-C₄alkyl, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂ and -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl;

R₂₀ is hydrogen, C₁-C₆alkyl, C₁-C₆alkanoyl or -SO₂C₁-C₆alkyl;

L is independently chosen at each occurrence from a bond, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, S(O)_m, N(R_x), C(=O)N(R_x), N(R_x)C(=O), N(R_x)S(O)_m, S(O)_mN(R_x) and N[S(O)_mR_x]S(O)_m; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C₁-C₈alkyl; and

M is independently selected at each occurrence from (a) hydrogen; and (b) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), phenylC₀-C₄alkyl and (5- to 7-membered heterocycle)C₀-C₄alkyl, each of which is substituted with from 0 to 5 substituents independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, aminocarbonyl, aminoC₁-C₆alkyl and mono- and di-(C₁-C₆alkyl)amino.

71. A compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

A, B, E, D, G, W, X, Y and Z are independently CR₁ or N;

R₃ and R₄ are independently chosen from R₁;

R₁ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M;

L is independently chosen at each occurrence from a bond, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, S(O)_m, N(R_x), C(=O)N(R_x), N(R_x)C(=O), N(R_x)S(O)_m, S(O)_mN(R_x) and N[S(O)_mR_x]S(O)_m; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C₁-C₈alkyl; and

M is independently selected at each occurrence from (a) hydrogen; and (b) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), phenylC₀-C₄alkyl and (5- to 7-membered heterocycle)C₀-C₄alkyl, each of which is substituted with from 0 to 5 substituents independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, aminocarbonyl, aminoC₁-C₆alkyl and mono- and di-(C₁-C₆alkyl)amino.

72. A compound or pharmaceutically acceptable form thereof according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71, wherein the compound has an IC₅₀ value of 100 nanomolar or less in a capsaicin receptor calcium mobilization assay.

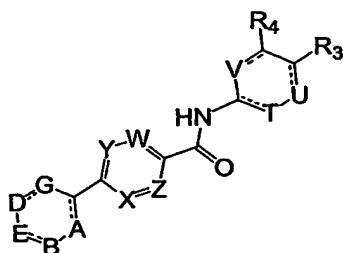
73. A compound or pharmaceutically acceptable form thereof according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71, wherein the compound has an IC₅₀ value of 10 nanomolar or less in a capsaicin receptor calcium mobilization assay.

74. A compound or pharmaceutically acceptable form thereof according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71, wherein the compound has an IC₅₀ value of 1 nanomolar or less in a capsaicin receptor calcium mobilization assay.

75. A pharmaceutical composition, comprising at least one compound or pharmaceutically acceptable form thereof according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71 in combination with a physiologically acceptable carrier or excipient.

76. A pharmaceutical composition according to claim 75, wherein the composition is formulated as an injectible fluid, an aerosol, a cream, a gel, a pill, a capsule, a syrup or a transdermal patch.

77. A method for reducing calcium conductance of a cellular capsaicin receptor, comprising contacting a cell expressing a capsaicin receptor with at least one compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

each --- independently represents a single or double bond;

either: (a) A, B and E are independently CR_1 , $\text{C}(\text{R}_1)_2$, NR_1 or N; or

(b) B is joined with A or E to form a fused 5- to 8-membered partially saturated ring that is substituted with from 0 to 3 substituents independently selected from R_1 , and the other of A or E is CR_1 , $\text{C}(\text{R}_1)_2$, NR_1 or N;

D and G are independently CR_1 , $\text{C}(\text{R}_1)_2$, NR_1 or N;

W, X, Y and Z are independently CR_1 or N;

T, U and V are independently CR_8 , $\text{C}(\text{R}_8)_2$, N or NH ;

R_1 is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M;

R_3 and R_4 are:

(a) independently chosen from R_8 ; or

(b) taken together to form a fused ring selected from 5- to 8-membered carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings and dioxane, each of which fused ring is substituted with from 0 to 3 substituents independently selected from halogen, hydroxy, amino, nitro, cyano, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, $\text{C}_1\text{-C}_6\text{alkoxy}$, $\text{C}_1\text{-C}_6\text{haloalkoxy}$, $\text{C}_1\text{-C}_6\text{alkanoyl}$, $\text{C}_2\text{-C}_6\text{alkyl ether}$, mono- and di- $(\text{C}_1\text{-C}_6\text{alkyl})\text{amino}$, $\text{C}_0\text{-C}_4\text{alkyl}$, $\text{-N(H)SO}_2\text{C}_1\text{-C}_6\text{alkyl}$, $\text{-N(SO}_2\text{C}_1\text{-C}_6\text{alkyl)}_2$, and $\text{-N(C}_1\text{-C}_6\text{alkyl)SO}_2\text{C}_1\text{-C}_6\text{alkyl}$;

R_8 is independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, $\text{C}_1\text{-C}_6\text{alkoxy}$, $\text{C}_1\text{-C}_6\text{haloalkoxy}$, $\text{C}_1\text{-C}_6\text{alkanoyl}$, $\text{C}_2\text{-C}_6\text{alkyl ether}$, mono- and di- $(\text{C}_1\text{-C}_6\text{alkyl})\text{amino}$, $\text{-N(H)SO}_2\text{C}_1\text{-C}_6\text{alkyl}$, $\text{-N(SO}_2\text{C}_1\text{-C}_6\text{alkyl)}_2$, $\text{-N(C}_1\text{-C}_6\text{alkyl)SO}_2\text{C}_1\text{-C}_6\text{alkyl}$, and 5 to 7 membered heteroalicyclic and heteroaryl rings;

L is independently chosen at each occurrence from a bond, O, C(=O) , OC(=O) , C(=O)O , O-C(=O)O , S(O)_m , $\text{N(R}_x\text{)}$, $\text{C(=O)N(R}_x\text{)}$, $\text{N(R}_x\text{)C(=O)}$, $\text{N(R}_x\text{)S(O)}_m$, $\text{S(O)}_m\text{N(R}_x\text{)}$ and $\text{N[S(O)}_m\text{R}_x\text{]S(O)}_m$; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and $\text{C}_1\text{-C}_8\text{alkyl}$; and

M is independently selected at each occurrence from (a) hydrogen; and (b) $\text{C}_1\text{-C}_8\text{alkyl}$, $\text{C}_2\text{-C}_8\text{alkenyl}$, $\text{C}_2\text{-C}_8\text{alkynyl}$, mono- and di- $(\text{C}_1\text{-C}_4\text{alkyl})\text{amino}$, $\text{C}_0\text{-C}_4\text{alkyl}$, phenyl $\text{C}_0\text{-C}_4\text{alkyl}$, (5-membered heteroaryl) $\text{C}_0\text{-C}_4\text{alkyl}$ and (5- to 7-membered heterocycloalkyl) $\text{C}_0\text{-C}_4\text{alkyl}$, each of which is substituted with from 0 to 5 substituents independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, $\text{C}_1\text{-C}_6\text{alkoxy}$, $\text{C}_1\text{-C}_6\text{haloalkoxy}$, aminocarbonyl, amino $\text{C}_1\text{-C}_6\text{alkyl}$ and mono- and di- $(\text{C}_1\text{-C}_6\text{alkyl})\text{amino}$;

and thereby reducing calcium conductance of the capsaicin receptor.

78. A method according to claim 77, wherein the compound is a compound according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71.

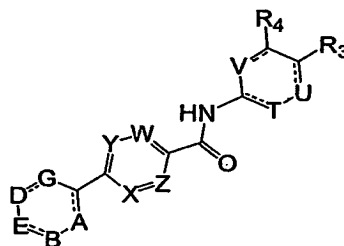
79. A method according to claim 77, wherein the cell is a neuronal cell that is contacted *in vivo* in an animal.

80. A method according to claim 79, wherein during contact the compound is present within a body fluid of the animal.

81. A method according to claim 79, wherein the animal is a human.

82. A method according to claim 79, wherein the compound is administered orally.

83. A method for inhibiting binding of vanilloid ligand to a capsaicin receptor *in vitro*, the method comprising contacting capsaicin receptor with at least one compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

each \equiv independently represents a single or double bond;

either: (a) A, B and E are independently CR₁, C(R₁)₂, NR₁ or N; or

(b) B is joined with A or E to form a fused 5- to 8-membered partially saturated ring that is substituted with from 0 to 3 substituents independently selected from R₁, and the other of A or E is CR₁, C(R₁)₂, NR₁ or N;

D and G are independently CR₁, C(R₁)₂, NR₁ or N;

W, X, Y and Z are independently CR₁ or N;

T, U and V are independently CR₈, C(R₈)₂, N or NH;

R₁ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M;

R₃ and R₄ are:

(a) independently chosen from R₈; or

(b) taken together to form a fused ring selected from 5- to 8-membered carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings and dioxane, each of which fused ring is substituted with from 0 to 3 substituents independently selected from halogen, hydroxy, amino, nitro, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)amino, C₀-C₄alkyl, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂, and -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl;

R₈ is independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)amino, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂, -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl, and 5 to 7 membered heteroalicyclic and heteroaryl rings;

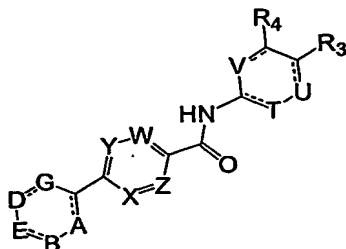
L is independently chosen at each occurrence from a bond, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, S(O)_m, N(R_x), C(=O)N(R_x), N(R_x)C(=O), N(R_x)S(O)_m, S(O)_mN(R_x) and N[S(O)_mR_x]S(O)_m; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C₁-C₈alkyl; and

M is independently selected at each occurrence from (a) hydrogen; and (b) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), phenylC₀-C₄alkyl, (5-membered heteroaryl)C₀-C₄alkyl and (5- to 7-membered heterocycloalkyl)C₀-C₄alkyl, each of which is substituted with from 0 to 5 substituents independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, aminocarbonyl, aminoC₁-C₆alkyl and mono- and di-(C₁-C₆alkyl)amino;

under conditions and in an amount sufficient to detectably inhibit vanilloid ligand binding to capsaicin receptor.

84. A method according to claim 83, wherein the compound is a compound according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71.

85. A method for inhibiting binding of vanilloid ligand to capsaicin receptor in a patient, comprising contacting cells expressing capsaicin receptor in the patient with a compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

each ---- independently represents a single or double bond;

either: (a) A, B and E are independently CR₁, C(R₁)₂, NR₁ or N; or

(b) B is joined with A or E to form a fused 5- to 8-membered partially saturated ring that is substituted with from 0 to 3 substituents independently selected from R₁, and the other of A or E is CR₁, C(R₁)₂, NR₁ or N;

D and G are independently CR₁, C(R₁)₂, NR₁ or N;

W, X, Y and Z are independently CR₁ or N;

T, U and V are independently CR₈, C(R₈)₂, N or NH;

R₁ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M;

R₃ and R₄ are:

(a) independently chosen from R₈; or

(b) taken together to form a fused ring selected from 5- to 8-membered carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings and dioxane, each of which fused ring is substituted with from 0 to 3 substituents independently selected from halogen, hydroxy, amino, nitro, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)amino, C₀-C₄alkyl, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂, and -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl;

R₈ is independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)amino, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂, and -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl, and 5 to 7 membered heteroalicyclic and heteroaryl rings;

L is independently chosen at each occurrence from a bond, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, S(O)_m, N(R_x), C(=O)N(R_x), N(R_x)C(=O), N(R_x)S(O)_m, S(O)_mN(R_x) and N[S(O)_mR_x]S(O)_m; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C₁-C₈alkyl; and

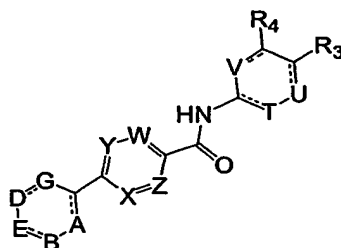
M is independently selected at each occurrence from (a) hydrogen; and (b) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), phenylC₀-C₄alkyl, (5-membered heteroaryl)C₀-C₄alkyl and (5- to 7-membered heterocycloalkyl)C₀-C₄alkyl, each of which is substituted with from 0 to 5 substituents independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, aminocarbonyl, aminoC₁-C₆alkyl and mono- and di-(C₁-C₆alkyl)amino.

in an amount sufficient to detectably inhibit vanilloid ligand binding to cells expressing a cloned capsaicin receptor *in vitro*, and thereby inhibiting binding of vanilloid ligand to the capsaicin receptor in the patient.

86. A method according to claim 85, wherein the compound is a compound according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71.

87. A method according to claim 85, wherein the patient is a human.

88. A method for treating a condition responsive to capsaicin receptor modulation in a patient, comprising administering to the patient a capsaicin receptor modulatory amount of at least one compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

each --- independently represents a single or double bond;

either: (a) A, B and E are independently CR_1 , $\text{C}(\text{R}_1)_2$, NR_1 or N; or

(b) B is joined with A or E to form a fused 5- to 8-membered partially saturated ring that is substituted with from 0 to 3 substituents independently selected from R_1 , and the other of A or E is CR_1 , $\text{C}(\text{R}_1)_2$, NR_1 or N;

D and G are independently CR_1 , $\text{C}(\text{R}_1)_2$, NR_1 or N;

W, X, Y and Z are independently CR_1 or N;

T, U and V are independently CR_8 , $\text{C}(\text{R}_8)_2$, N or NH ;

R_1 is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M;

R_3 and R_4 are:

(a) independently chosen from R_8 ; or

(b) taken together to form a fused ring selected from 5- to 8-membered carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings and dioxane, each of which fused ring is substituted with from 0 to 3 substituents independently selected from halogen, hydroxy, amino, nitro, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 -

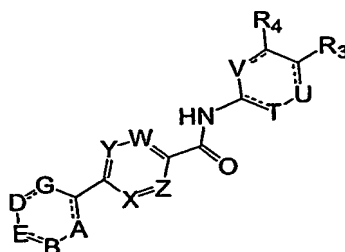
C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)aminoC₀-C₄alkyl, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂, and -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl;
 R₈ is independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)amino, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂, -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl, and 5 to 7 membered heteroalicyclic and heteroaryl rings;
 L is independently chosen at each occurrence from a bond, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, S(O)_m, N(R_x), C(=O)N(R_x), N(R_x)C(=O), N(R_x)S(O)_m, S(O)_mN(R_x) and N[S(O)_mR_x]S(O)_m; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C₁-C₈alkyl; and
 M is independently selected at each occurrence from (a) hydrogen; and (b) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), phenylC₀-C₄alkyl, (5-membered heteroaryl)C₀-C₄alkyl and (5- to 7-membered heterocycloalkyl)C₀-C₄alkyl, each of which is substituted with from 0 to 5 substituents independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, aminocarbonyl, aminoC₁-C₆alkyl and mono- and di-(C₁-C₆alkyl)amino.
 and thereby alleviating the condition in the patient.

89. A method according to claim 88, wherein the compound is a compound according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71.

90. A method according to claim 88, wherein the patient is suffering from (i) exposure to capsaicin, (ii) burn or irritation due to exposure to heat, (iii) burns or irritation due to exposure to light, (iv) burn, bronchoconstriction or irritation due to exposure to tear gas, air pollutants or pepper spray, or (v) burn or irritation due to exposure to acid.

91. A method according to claim 88, wherein the condition is treating asthma or chronic obstructive pulmonary disease.

92. A method for treating pain in a patient, comprising administering to a patient suffering from pain a capsaicin receptor modulatory amount of at least one compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

each --- independently represents a single or double bond;

either: (a) A, B and E are independently CR_1 , $\text{C}(\text{R}_1)_2$, NR_1 or N; or

(b) B is joined with A or E to form a fused 5- to 8-membered partially saturated ring that is substituted with from 0 to 3 substituents independently selected from R_1 , and the other of A or E is CR_1 , $\text{C}(\text{R}_1)_2$, NR_1 or N;

D and G are independently CR_1 , $\text{C}(\text{R}_1)_2$, NR_1 or N;

W, X, Y and Z are independently CR_1 or N;

T, U and V are independently CR_8 , $\text{C}(\text{R}_8)_2$, N or NH ;

R_1 is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M;

R_3 and R_4 are:

(a) independently chosen from R_8 ; or

(b) taken together to form a fused ring selected from 5- to 8-membered carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings and dioxane, each of which fused ring is substituted with from 0 to 3 substituents independently selected from halogen, hydroxy, amino, nitro, cyano, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkoxy, $\text{C}_1\text{-C}_6$ alkanoyl, $\text{C}_2\text{-C}_6$ alkyl ether, mono- and di- $(\text{C}_1\text{-C}_6\text{alkyl})$ amino, $\text{C}_0\text{-C}_4$ alkyl, $-\text{N}(\text{H})\text{SO}_2\text{C}_1\text{-C}_6\text{alkyl}$, $-\text{N}(\text{SO}_2\text{C}_1\text{-C}_6\text{alkyl})_2$, and $-\text{N}(\text{C}_1\text{-C}_6\text{alkyl})\text{SO}_2\text{C}_1\text{-C}_6\text{alkyl}$;

R_8 is independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkoxy, $\text{C}_1\text{-C}_6$ alkanoyl, $\text{C}_2\text{-C}_6$ alkyl ether, mono- and di- $(\text{C}_1\text{-C}_6\text{alkyl})$ amino, $-\text{N}(\text{H})\text{SO}_2\text{C}_1\text{-C}_6\text{alkyl}$, $-\text{N}(\text{SO}_2\text{C}_1\text{-C}_6\text{alkyl})_2$, $-\text{N}(\text{C}_1\text{-C}_6\text{alkyl})\text{SO}_2\text{C}_1\text{-C}_6\text{alkyl}$, and 5 to 7 membered heteroalicyclic and heteroaryl rings;

L is independently chosen at each occurrence from a bond, O, $\text{C}(=\text{O})$, $\text{OC}(=\text{O})$, $\text{C}(=\text{O})\text{O}$, $\text{O}-\text{C}(=\text{O})\text{O}$, $\text{S}(\text{O})_m$, $\text{N}(\text{R}_x)$, $\text{C}(=\text{O})\text{N}(\text{R}_x)$, $\text{N}(\text{R}_x)\text{C}(=\text{O})$, $\text{N}(\text{R}_x)\text{S}(\text{O})_m$, $\text{S}(\text{O})_m\text{N}(\text{R}_x)$ and $\text{N}[\text{S}(\text{O})_m\text{R}_x]\text{S}(\text{O})_m$; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and $\text{C}_1\text{-C}_8$ alkyl; and

M is independently selected at each occurrence from (a) hydrogen; and (b) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), phenylC₀-C₄alkyl, (5-membered heteroaryl)C₀-C₄alkyl and (5- to 7-membered heterocycloalkyl)C₀-C₄alkyl, each of which is substituted with from 0 to 5 substituents independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, aminocarbonyl, aminoC₁-C₆alkyl and mono- and di-(C₁-C₆alkyl)amino.

and thereby alleviating pain in the patient.

93. A method according to claim 92, wherein the compound is a compound according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71.

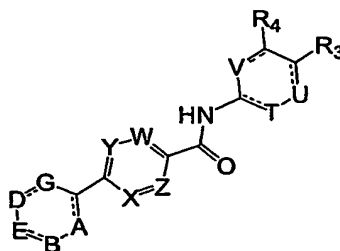
94. A method according to claim 92, wherein the patient is suffering from neuropathic pain.

95. A method according to claim 92, wherein the patient is suffering from mechanical pain.

96. A method according to claim 92, wherein the pain is associated with a condition selected from: postmastectomy pain syndrome, stump pain, phantom limb pain, oral neuropathic pain, toothache, postherpetic neuralgia, diabetic neuropathy, reflex sympathetic dystrophy, trigeminal neuralgia, osteoarthritis, rheumatoid arthritis, fibromyalgia, Guillain-Barre syndrome, meralgia paresthetica, burning-mouth syndrome, bilateral peripheral neuropathy, causalgia, neuritis, neuronitis, neuralgia, AIDS-related neuropathy, MS-related neuropathy, spinal cord injury-related pain, surgery-related pain, musculoskeletal pain, back pain, headache, migraine, angina, labor, hemorrhoids, dyspepsia, Charcot's pains, intestinal gas, menstruation, cancer, venom exposure, irritable bowel syndrome, inflammatory bowel disease, and/or trauma.

97. A method according to claim 92, wherein the patient is a human.

98. A method for treating itch in a patient, comprising administering to a patient a capsaicin receptor modulatory amount of a compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

each --- independently represents a single or double bond;

either: (a) A, B and E are independently CR₁, C(R₁)₂, NR₁ or N; or

(b) B is joined with A or E to form a fused 5- to 8-membered partially saturated ring that is substituted with from 0 to 3 substituents independently selected from R₁, and the other of A or E is CR₁, C(R₁)₂, NR₁ or N;

D and G are independently CR₁, C(R₁)₂, NR₁ or N;

W, X, Y and Z are independently CR₁ or N;

T, U and V are independently CR₈, C(R₈)₂, N or NH;

R₁ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M;

R₃ and R₄ are:

(a) independently chosen from R₈; or

(b) taken together to form a fused ring selected from 5- to 8-membered carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings and dioxane, each of which fused ring is substituted with from 0 to 3 substituents independently selected from halogen, hydroxy, amino, nitro, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)amino, C₀-C₄alkyl, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂, and -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl;

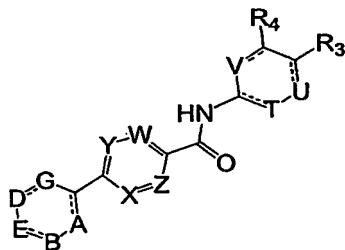
R₈ is independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)amino, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂, -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl, and 5 to 7 membered heteroalicyclic and heteroaryl rings;

L is independently chosen at each occurrence from a bond, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, S(O)_m, N(R_x), C(=O)N(R_x), N(R_x)C(=O), N(R_x)S(O)_m, S(O)_mN(R_x) and

$N[S(O)_mR_x]S(O)_m$; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C_1 - C_8 alkyl; and M is independently selected at each occurrence from (a) hydrogen; and (b) C_1 - C_8 alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, mono- and di- $(C_1$ - C_4 alkyl)amino(C_0 - C_4 alkyl), phenyl C_0 - C_4 alkyl, (5-membered heteroaryl) C_0 - C_4 alkyl and (5- to 7-membered heterocycloalkyl) C_0 - C_4 alkyl, each of which is substituted with from 0 to 5 substituents independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, aminocarbonyl, amino C_1 - C_6 alkyl and mono- and di- $(C_1$ - C_6 alkyl)amino. and thereby alleviating itch in the patient.

99. A method according to claim 98, wherein the compound is a compound according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71.

100. A method for treating cough or hiccup in a patient, comprising administering to a patient a capsaicin receptor modulatory amount of a compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

each --- independently represents a single or double bond;

either: (a) A, B and E are independently CR_1 , $C(R_1)_2$, NR_1 or N; or

(b) B is joined with A or E to form a fused 5- to 8-membered partially saturated ring that is substituted with from 0 to 3 substituents independently selected from R_1 , and the other of A or E is CR_1 , $C(R_1)_2$, NR_1 or N;

D and G are independently CR_1 , $C(R_1)_2$, NR_1 or N;

W, X, Y and Z are independently CR_1 or N;

T, U and V are independently CR_3 , $C(R_3)_2$, N or NH;

R_1 is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M;

R_3 and R_4 are:

(a) independently chosen from R_8 ; or

(b) taken together to form a fused ring selected from 5- to 8-membered carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings and dioxane, each of which fused ring is substituted with from 0 to 3 substituents independently selected from halogen, hydroxy, amino, nitro, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)amino, C₀-C₄alkyl, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂, and -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl;

R₈ is independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)amino, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂ and -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl, and 5 to 7 membered heteroalicyclic and heteroaryl rings;

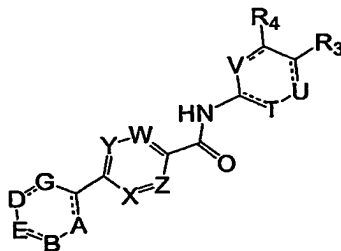
L is independently chosen at each occurrence from a bond, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, S(O)_m, N(R_x), C(=O)N(R_x), N(R_x)C(=O), N(R_x)S(O)_m, S(O)_mN(R_x) and N[S(O)_mR_x]S(O)_m; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C₁-C₈alkyl; and

M is independently selected at each occurrence from (a) hydrogen; and (b) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), phenylC₀-C₄alkyl, (5-membered heteroaryl)C₀-C₄alkyl and (5- to 7-membered heterocycloalkyl)C₀-C₄alkyl, each of which is substituted with from 0 to 5 substituents independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, aminocarbonyl, aminoC₁-C₆alkyl and mono- and di-(C₁-C₆alkyl)amino.

and thereby alleviating cough or hiccup in the patient.

101. A method according to claim 100, wherein the compound is a compound according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71.

102. A method for treating urinary incontinence in a patient, comprising administering to a patient a capsaicin receptor modulatory amount of a compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

each --- independently represents a single or double bond;

either: (a) A, B and E are independently CR_1 , $\text{C}(\text{R}_1)_2$, NR_1 or N; or

(b) B is joined with A or E to form a fused 5- to 8-membered partially saturated ring that is substituted with from 0 to 3 substituents independently selected from R_1 , and the other of A or E is CR_1 , $\text{C}(\text{R}_1)_2$, NR_1 or N;

D and G are independently CR_1 , $\text{C}(\text{R}_1)_2$, NR_1 or N;

W, X, Y and Z are independently CR_1 or N;

T, U and V are independently CR_8 , $\text{C}(\text{R}_8)_2$, N or NH ;

R_1 is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M;

R_3 and R_4 are:

(a) independently chosen from R_8 ; or

(b) taken together to form a fused ring selected from 5- to 8-membered carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings and dioxane, each of which fused ring is substituted with from 0 to 3 substituents independently selected from halogen, hydroxy, amino, nitro, cyano, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, $\text{C}_1\text{-C}_6\text{alkoxy}$, $\text{C}_1\text{-C}_6\text{haloalkoxy}$, $\text{C}_1\text{-C}_6\text{alkanoyl}$, $\text{C}_2\text{-C}_6\text{alkyl ether}$, mono- and di- $(\text{C}_1\text{-C}_6\text{alkyl})\text{amino}$, $\text{C}_0\text{-C}_4\text{alkyl}$, $\text{-N(H)SO}_2\text{C}_1\text{-C}_6\text{alkyl}$, $\text{-N(SO}_2\text{C}_1\text{-C}_6\text{alkyl)}_2$, and $\text{-N(C}_1\text{-C}_6\text{alkyl)SO}_2\text{C}_1\text{-C}_6\text{alkyl}$;

R_8 is independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, $\text{C}_1\text{-C}_6\text{alkoxy}$, $\text{C}_1\text{-C}_6\text{haloalkoxy}$, $\text{C}_1\text{-C}_6\text{alkanoyl}$, $\text{C}_2\text{-C}_6\text{alkyl ether}$, mono- and di- $(\text{C}_1\text{-C}_6\text{alkyl})\text{amino}$, $\text{-N(H)SO}_2\text{C}_1\text{-C}_6\text{alkyl}$, $\text{-N(SO}_2\text{C}_1\text{-C}_6\text{alkyl)}_2$, $\text{-N(C}_1\text{-C}_6\text{alkyl)SO}_2\text{C}_1\text{-C}_6\text{alkyl}$, and 5 to 7 membered heteroalicyclic and heteroaryl rings;

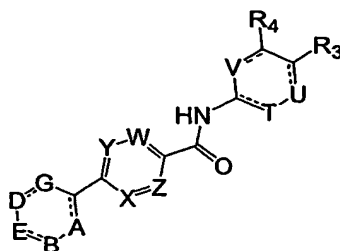
L is independently chosen at each occurrence from a bond, O, C(=O) , OC(=O) , C(=O)O , O-C(=O)O , S(O)_m , $\text{N(R}_x\text{)}$, $\text{C(=O)N(R}_x\text{)}$, $\text{N(R}_x\text{)C(=O)}$, $\text{N(R}_x\text{)S(O)}_m$, $\text{S(O)}_m\text{N(R}_x\text{)}$ and $\text{N[S(O)}_m\text{R}_x\text{]S(O)}_m$; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and $\text{C}_1\text{-C}_8\text{alkyl}$; and

M is independently selected at each occurrence from (a) hydrogen; and (b) $\text{C}_1\text{-C}_8\text{alkyl}$, $\text{C}_2\text{-C}_8\text{alkenyl}$, $\text{C}_2\text{-C}_8\text{alkynyl}$, mono- and di- $(\text{C}_1\text{-C}_4\text{alkyl})\text{amino}$, $(\text{C}_0\text{-C}_4\text{alkyl})$, $\text{phenylC}_0\text{-C}_4\text{alkyl}$, $(5\text{-membered heteroaryl})\text{C}_0\text{-C}_4\text{alkyl}$ and $(5\text{- to } 7\text{-membered heterocycloalkyl})\text{C}_0\text{-C}_4\text{alkyl}$, each of which is substituted with from 0 to 5 substituents independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, $\text{C}_1\text{-C}_6\text{alkyl}$, $\text{C}_1\text{-C}_6\text{haloalkyl}$, $\text{C}_1\text{-C}_6\text{alkoxy}$, $\text{C}_1\text{-C}_6\text{haloalkoxy}$, aminocarbonyl, $\text{aminoC}_1\text{-C}_6\text{alkyl}$ and mono- and di- $(\text{C}_1\text{-C}_6\text{alkyl})\text{amino}$;

and thereby alleviating urinary incontinence in the patient.

103. A method according to claim 102, wherein the compound is a compound according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71.

104. A method for promoting weight loss in an obese patient, comprising administering to a patient a capsaicin receptor modulatory amount of a compound of the formula:



or a pharmaceutically acceptable form thereof, wherein:

each --- independently represents a single or double bond;

either: (a) A, B and E are independently CR₁, C(R₁)₂, NR₁ or N; or

(b) B is joined with A or E to form a fused 5- to 8-membered partially saturated ring that is substituted with from 0 to 3 substituents independently selected from R₁, and the other of A or E is CR₁, C(R₁)₂, NR₁ or N;

D and G are independently CR₁, C(R₁)₂, NR₁ or N;

W, X, Y and Z are independently CR₁ or N;

T, U and V are independently CR₈, C(R₈)₂, N or NH;

R₁ is independently chosen at each occurrence from halogen, cyano, nitro and groups of the formula L-M;

R₃ and R₄ are:

(a) independently chosen from R₈; or

(b) taken together to form a fused ring selected from 5- to 8-membered carbocyclic rings, 5-membered heterocyclic rings, 7-membered heterocyclic rings and dioxane, each of which fused ring is substituted with from 0 to 3 substituents independently selected from halogen, hydroxy, amino, nitro, cyano, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-C₆alkyl ether, mono- and di-(C₁-C₆alkyl)amino, C₀-C₄alkyl, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂, and -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl;

R₈ is independently chosen at each occurrence from hydrogen, halogen, hydroxy, amino, cyano, nitro, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₁-C₆alkanoyl, C₂-

C₆alkyl ether, mono- and di-(C₁-C₆alkyl)amino, -N(H)SO₂C₁-C₆alkyl, -N(SO₂C₁-C₆alkyl)₂, -N(C₁-C₆alkyl)SO₂C₁-C₆alkyl, and 5 to 7 membered heteroalicyclic and heteroaryl rings;

L is independently chosen at each occurrence from a bond, O, C(=O), OC(=O), C(=O)O, O-C(=O)O, S(O)_m, N(R_x), C(=O)N(R_x), N(R_x)C(=O), N(R_x)S(O)_m, S(O)_mN(R_x) and N[S(O)_mR_x]S(O)_m; wherein m is independently selected at each occurrence from 0, 1 and 2; and R_x is independently selected at each occurrence from hydrogen and C₁-C₈alkyl; and

M is independently selected at each occurrence from (a) hydrogen; and (b) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, mono- and di-(C₁-C₄alkyl)amino(C₀-C₄alkyl), phenylC₀-C₄alkyl, (5-membered heteroaryl)C₀-C₄alkyl and (5- to 7-membered heterocycloalkyl)C₀-C₄alkyl, each of which is substituted with from 0 to 5 substituents independently selected from halogen, hydroxy, cyano, nitro, amino, oxo, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, aminocarbonyl, aminoC₁-C₆alkyl and mono- and di-(C₁-C₆alkyl)amino; and thereby promoting weight loss in the patient.

105. A method according to claim 104, wherein the compound is a compound according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71.

106. A compound or pharmaceutically acceptable form thereof according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71, wherein the compound or pharmaceutically acceptable form thereof is radiolabeled.

107. A method for determining the presence or absence of capsaicin receptor in a sample, comprising the steps of:

- (a) contacting a sample with a compound or pharmaceutically acceptable form thereof according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71 under conditions that permit binding of the compound to capsaicin receptor; and
- (b) detecting a level of the compound bound to capsaicin receptor, and therefrom determining the presence or absence of capsaicin receptor in the sample.

108. A method according to claim 107, wherein the compound is a radiolabeled compound according to claim 106, and wherein the step of detection comprises the steps of:

- (i) separating unbound compound from bound compound; and
- (ii) detecting the presence or absence of bound compound in the sample.

109. A packaged pharmaceutical preparation, comprising:
- (a) a pharmaceutical composition according to claim 75 in a container; and
 - (b) instructions for using the composition to treat pain.
110. A packaged pharmaceutical preparation, comprising:
- (a) a pharmaceutical composition according to claim 75 in a container; and
 - (b) instructions for using the composition to treat cough or hiccup.
111. A packaged pharmaceutical preparation, comprising:
- (a) a pharmaceutical composition according to claim 75 in a container; and
 - (b) instructions for using the composition to treat urinary incontinence.
112. A packaged pharmaceutical preparation, comprising:
- (a) a pharmaceutical composition according to claim 75 in a container; and
 - (b) instructions for using the composition to treat obesity.
113. Use of a compound according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71 as a medicament for the treatment of a patient suffering from a condition responsive to capsaicin receptor modulation.
114. Use of a compound according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71 as a medicament for the treatment of a patient suffering from a condition responsive to capsaicin receptor modulation selected from (i) exposure to capsaicin, (ii) burn or irritation due to exposure to heat, (iii) burns or irritation due to exposure to light, (iv) burn, bronchoconstriction or irritation due to exposure to tear gas, air pollutants or pepper spray, or (v) burn or irritation due to exposure to acid.
115. Use of a compound according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71 as a medicament for the treatment of a patient suffering from to pain.
116. Use of a compound according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71 as a medicament for the treatment of a patient suffering from neuropathic pain associated with a condition selected from: postmastectomy pain syndrome, stump pain, phantom limb pain, oral neuropathic pain, toothache, postherpetic neuralgia, diabetic neuropathy, reflex sympathetic

dystrophy, trigeminal neuralgia, osteoarthritis, rheumatoid arthritis, fibromyalgia, Guillain-Barre syndrome, meralgia paresthetica, burning-mouth syndrome, bilateral peripheral neuropathy, causalgia, neuritis, neuronitis, neuralgia, AIDS-related neuropathy, MS-related neuropathy, spinal cord injury-related pain, surgery-related pain, musculoskeletal pain, back pain, headache, migraine, angina, labor, hemorrhoids, dyspepsia, Charcot's pains, intestinal gas, menstruation, cancer, venom exposure, irritable bowel syndrome, inflammatory bowel disease and trauma.

117. Use of a compound according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71 as a medicament for the treatment of a patient suffering from or susceptible to an itch.

118. Use of a compound according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71 as a medicament for the treatment of a patient suffering from or susceptible to urinary incontinence.

119. Use of a compound according to any one of claims 1, 17, 30, 45, 60, 65, 70 or 71 as a medicament for promoting weight loss in an obese patient.

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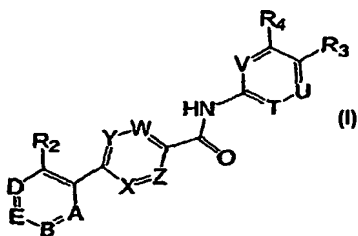
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For two-letter codes and other abbreviations, refer to the "Guid-
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(54) Title: SUBSTITUTED BIPHENYL-4-CARBOXYLIC ACID ARYLAMIDE ANALOGUES AS CAPSAICIN RECEPTOR MODULATORS



(57) Abstract: Substituted biphenyl-4-carboxylic acid arylamide analogues of the formula (I) capable of modulating receptor activity, are provided. Such ligands may be used to modulate receptor activity *in vivo* or *in vitro*, and are particularly useful in the treatment of pain and other conditions associated with receptor activation in humans, domesticated companion animals and livestock animals. Pharmaceutical compositions and methods for treating such disorders are provided, as are methods for using such ligands for receptor localization studies.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/40878

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D213/61 C07C235/64 C07D213/82 C07D213/26 C07D213/48
C07D405/12 C07D213/73 C07D211/34 C07D213/76 A61K31/44
A61P25/00 C07D417/12 C07D401/12 C07D405/04 C07D405/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 496 378 A (THOMAE GMBH DR K) 29 July 1992 (1992-07-29) example 10(13)claims 1,7-9	71,75
X	EP 0 480 258 A (BAYER AG) 15 April 1992 (1992-04-15) claim 1; examples 478,479,493,494	71,75
X	SIGMAN, MICHAEL E. ET AL: "Aroylnitrenes with singlet ground states: photochemistry of acetyl-substituted aroyl and aryloxycarbonyl azides" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , 110(13), 4297-305 CODEN: JACSAT; ISSN: 0002-7863, 1988, XP002289185 page 4305 N-cyclohexyl-4-acetyl-4'-biphenyl- carboxylic acid amide	71
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/40878

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KEIR W F ET AL: "Ethyl amidinoacetates in the synthesis of pyrazines" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, CHEMICAL SOCIETY. LETCWORTH, GB, 1978, pages 1002-1006, XP002284500 ISSN: 0300-922X compound 3t	71
X	U. LUECKING ET AL.: "Self-folding cavitanads of nanoscale dimensions" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 122, no. 37, 2000, pages 8880-8889, XP002289464 USAMERICAN CHEMICAL SOCIETY, WASHINGTON, DC. compound 12	71
X	PREVOT-HALTER, ISABELLE ET AL: "Assembling Organic Receptors around Transition Metal Templates: Functionalized Catechols and Dioxomolybdenum(VI) for the Recognition of Dicarboxylic Acids" JOURNAL OF ORGANIC CHEMISTRY, VOL. 62, NO. 7, 1997, PAGES 2186-2192CODEN: JOCEAH; ISSN: 0022-3263, 1997, XP002289184 compounds 1 and 10	1
A	WO 03/068749 A (MITCHELL DARREN JASON ; RAMI HARSHAD KANTILAL (GB); GLAXO GROUP LTD (G) 21 August 2003 (2003-08-21) claims 1-9; examples	1-119
A	WO 02/08221 A (BAKTHAVATCHALAM RAJAGOPAL ; DESIMONE ROBERT W (US); NEUROGEN CORP (US)) 31 January 2002 (2002-01-31) the whole document	1-119
A	SZALLASI A ET AL: "VANILLOID (CAPSAICIN) RECEPTORS AND MECHANISMS" PHARMACOLOGICAL REVIEWS, WILLIAMS AND WILKINS INC., BALTIMORE, MD,, US, vol. 51, no. 2, 1999, pages 159-211, XP001105620 ISSN: 0031-6997 abstract	1,17,30, 45,60, 65,70, 71, 113-119

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 77-105 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 71 (part.)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to: claims 1-70, 72-119. The large number of relevant documents for claim 71 precludes a comprehensive search report.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/40878

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 77-105
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 77-105 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 71 (part.)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/40878

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